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CALCIUM METABOLISM IN IDIOPATHIC HYPERCALCAEMIA OF INFANCY WITH FAILURE TO THRIVE

BY

R. E. BONHAM CARTER, C. E. DENT, DOROTHY I. FOWLER
and CHRISTINE M. HARPER
From University College Hospital and Medical School, London

(RECEIVED FOR PUBLICATION JUNE 5, 1955)

As pointed out by a leader in the *Lancet* (1953), marasmus or 'teething' no longer satisfies paediatricians as a diagnosis for an infant's failure to thrive. The clinical studies of Lightwood and the biochemical work of Payne have recently shown that failure to thrive with constipation, hypotonia, polyuria, loss of appetite with occasional vomiting and intermittent urinary infection may be associated with at least two biochemical patterns, the first being that of renal acidosis (Lightwood, Payne and Black, 1953) and the second that of hypercalcaemia (Lightwood, 1952). Although the biochemical findings have now enabled these disease patterns to be identified from the ruck of marasmus and have led to hopeful therapeutic attempts to correct the biochemical abnormalities, the aetiology of both conditions remains in doubt.

The hypercalcaemic syndrome has apparently two forms, a commoner and milder form (Lightwood, 1952; Creery and Neill, 1954; Lowe, Henderson, Park and McGreal, 1954) and a more severe form (Fanconi, Girardet, Schlesinger, Butler and Black, 1952; Lowe *et al.*, 1954). The milder form has been attributed by Creery and Neill (1954) and others to excessive vitamin D or calcium intake and by Lowe *et al.* (1954) to hypersensitivity to vitamin D. Some evidence that individual differences occur in sensitivity to the toxic action of vitamin D has been summarized by Bicknell and Prescott (1942). The possibility, therefore, that either or both forms of hypercalcaemia are due not so much to an excessive intake but to an innate or induced sensitivity to vitamin D must also be considered.

In the hypercalcaemic syndrome an additional feature in some cases has been a systolic murmur which Bonham Carter, after investigating Lightwood's cases, has suggested might be associated with the hypertension and atheroma which accompanies this condition in some of its phases (unpublished observations). This was the immediate reason for the referral of the case described below.

In the present paper we describe metabolic studies on an infant with the milder form of the hypercalcaemic syndrome. We were especially concerned to investigate whether there is indeed an excessive sensitivity to vitamin D in this disease, also how far the metabolic abnormalities mimic an overdose of the vitamin and, finally, how far the symptoms might be due to the hypercalcaemia and might therefore respond to measures aimed at correcting this abnormality.

Case History

The child (Peter M.) was referred by Dr. Ellis of Romford to the Children's Department of University College Hospital because of failure to thrive with vomiting and a cough; he had observed a systolic murmur maximal in the pulmonary areas. The child was admitted to the children's ward on October 13, 1952. He was 9 months old and his history was of loss of weight for six weeks, with loss of appetite and vomiting between meals for the same period. The illness started with a cough, but his parents noticed that he had been flabby for seven weeks before this. His earlier history was uneventful. His birth weight was 7 lb. 8 oz. following a normal pregnancy and labour. He was breast fed for three months and then he was given 'ostermilk' and mixed feeding at 4½-5 months. His development was normal up to the time of his illness. Constipation was only slight and there was no evidence of an abnormally high intake of vitamin D.

The child was wasted and hypotonic but not dehydrated. The only other physical sign found was a systolic murmur, maximal in the pulmonary area. Investigations at that time showed haemoglobin 82%, W.B.C. 18,000, E.S.R. 45 mm./hr. The urine contained 0·1 parts per 1,000 of protein with numerous pus cells and gave a growth of *Proteus vulgaris*. There was tryptic activity in the stool. Radiographs showed some peribronchial changes in the lung fields, but no evidence of rickets. The bones were well calcified and of normal structure. The blood urea was 24 mg./100 ml.; calcium 13·8 mg./100 ml.; phosphatase 7·5 units (King-Armstrong). Total protein was 6·85 g./100 ml.; bicarbonate 26 mEq./l.; chlorides

102 mEq./l. These biochemical investigations led to a diagnosis of idiopathic hypercalcaemia.

From admission on October 13, 1952, until the beginning of December, the child remained in rather poor condition, but gained weight slowly from 6·25 to about 7·5 kg. The urine contained pus cells most of the time and grew at various times *Proteus vulgaris*, *Staph. albus*, and a mixed flora, being also sterile on occasion. He had several febrile attacks which were treated with various antibiotics without much success (Fig. 1). At

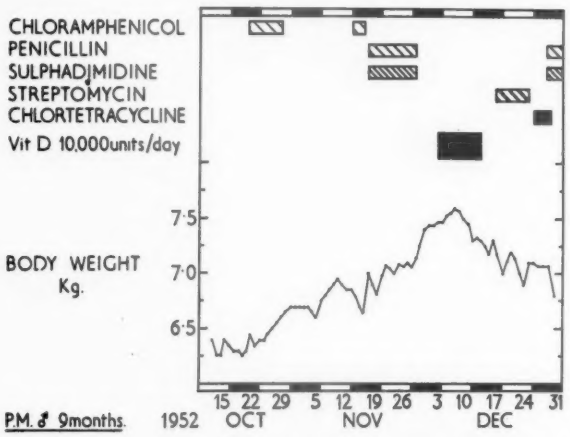

FIG. 1.—Weight curve while in the children's ward. It is noted that definite loss of weight followed 10 days on 10,000 units a day of vitamin D as calciferol. The use of antibiotic treatment is also shown as an indication of the child's repeated infections.

this time we began to suspect that vitamin D sensitivity was the cause of his disease. Because, therefore, of the lack of any definite improvement and doubts as to the future management of such a case, it was considered justifiable to administer a provocative small dose of vitamin D, which would settle once and for all whether he was sensitive to it and whether rigorous omission of it from the diet was a necessary part of his treatment. Therefore on December 1, 1952, he was given vitamin D, 10,000 units a day by mouth in the form of ¼ mg. a day of pure calciferol. The plasma calcium level had been 10·6 on November 21. On December 9 it had risen to 11·2. The results became known on December 12, and as his condition was beginning to deteriorate, vitamin D was stopped. The plasma calcium on December 13 was 11·9 mg./100 ml.

He had not shown any marked clinical changes during the 12 days when calciferol was given. However, soon after this his condition did appear to worsen markedly and a loss of weight became obvious (Fig. 1). This continued till by the end of December his body weight had fallen to 7·0 kg.; he was much more difficult to feed and he had become very miserable and hypotonic. Unfortunately no further serum calcium levels were determined during this period. We presume that they were raised as the next reading on January 4 was 11·4 mg./100 ml. Blood urea had been normal at 21 mg. % at the end of vitamin D administration on December 13; it rose to 30 mg. on December 19 and was still the same on the 30th. It was in this poor condition that he was transferred on January 1, 1953, to the metabolic ward.

In the metabolic ward a diet was arranged for him which contained 1,000 calories a day and included 500 ml. of milk, and was complete in salts and vitamins except that no vitamin D was added. This diet contained 610 mg. of calcium and was practically free from vitamin D. It was given in exactly measured quantities until February 27, 1953. However, at the intervals stated below, the milk was treated with ion exchange resin to exchange all the calcium (and other polyvalent metals) for sodium and potassium. Details of the diet are shown in Table 1.

TABLE 1

DIET GIVEN WHILE IN METABOLIC WARD

500 ml. milk (ordinary homogenized or decalcified, according to schedule described later)

250 ml. of high calorie supplement comprising:
100 g. glucose
22 g. (25 ml.) arachis oil
6·25 g. gum acacia
distilled water up to 250 ml. and the whole shaken till apparently homogeneous

250 ml. distilled water containing:
5 mg. aneurin
5 mg. riboflavine
50 mg. nicotinamide
50 mg. ascorbic acid
5 mg. pyridoxine
10 µg. vitamin B_{12}
0·1 ml. colliron (10% strength)

The daily diet above measured 1 l. and was given as five feeds of 200 ml. each. When the calcium-free diet was given (by using decalcified milk instead of ordinary milk), a supplement of 0·5 g. magnesium sulphate and 3 g. potassium chloride was made. The decalcified milk was prepared as described by Dent (1955).

On January 2 the calcium-free form of the diet was given (Fig. 2); on the 10th the calcium-containing form; on the 17th the calcium-free; on the 24th the calcium-containing; on February 7 the calcium-free; on the 21st the calcium-containing; on the 26th the calcium-free. By February 27 it was considered that adequate information had been obtained as to the effect of this quantity of calcium in the diet, so a new diet comprising more mixed food but limited to a daily intake of 200 mg. of calcium was given. This was an attempt to devise a diet suitable for taking at home. However, the calcium content appeared to be still too high, so it was limited to 100 mg. a day on March 15 and two days later raised to 200 mg. with an addition of 50 g. of 'all-bran' as a source of phytic acid. On this the child worsened and the calcium-free diet was begun again on March 22, 1953. After the clinical and biochemical improvement thus obtained a further attempt was made on April 8 to keep him on a mixed diet limited to 200 mg. of calcium, but with 50 g. of 'all-bran' a day. He continued on this until he went home on May 20, 1953.

While on these diets, repeated determinations of plasma calcium, phosphorus and urea were made and also daily body weighings and routine urine examinations. Calcium balance determinations were also done on four occasions during four-day collection periods, and further

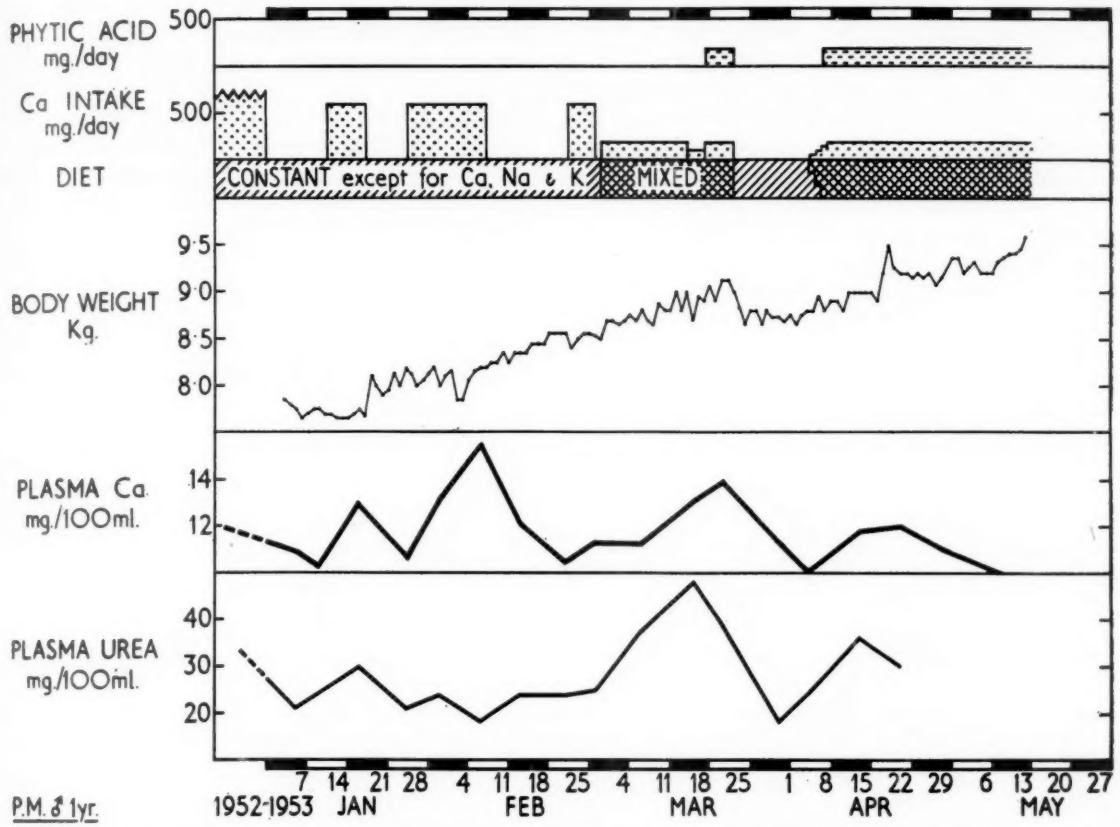

FIG. 2.—The extreme lability of the plasma calcium level should be noted. It rose rapidly whenever calcium was introduced into the diet. There is an embarrassing jump of body weight between periods shown in Fig. 1 and in this figure. This corresponds to some rehydration but we think it was mainly due to a change in the scales used in the two wards. We unfortunately omitted to investigate this at the time.

occasional 24-hour urine collections were also made for analysis of total calcium. During most of his time he was taking by mouth sulphadimidine, 0·25 g. b.d., as a prophylactic.

Methods

For collection of specimens of urine and faeces for the balance determinations the procedure of Black (1951) was followed.

Standard laboratory methods were used for the determinations of calcium (Clark and Collip, 1925), phosphorus and urea.

Results

Biochemical Changes and their Interpretation. The main results are summarized in the chart shown in Fig. 2. This shows clearly that the calcium-free diet readily reduced the plasma calcium levels to normal while the calcium-containing diet caused it to rise quickly to grossly abnormal levels. Plasma urea tended to rise and fall with the calcium level, but on the whole there was a gradual fall throughout the period on the standardized diet. There was a large rise in plasma urea when mixed feeding was begun. We presume that this was due to an increased protein intake since the intake was rather low, only 20 g. a day, on the standard diet. Clearly 200 mg. of calcium was too high an intake when first given, as the plasma calcium rose, and the addition of phytic acid for a few days did not appear to have much effect. When this diet was repeated later, however, it was tolerated by the patient, who showed this time only a small temporary rise in the plasma

TABLE 2

CALCIUM INTAKE AND OUTPUT FROM JANUARY TO APRIL, 1953

Date (inclusive)	Urine Ca (mg./day)	Stool Ca (mg./day)	Diet Ca (mg./day)	Ca Balance (mg./day)
Jan. 7-10	84	108	0	−192
Jan. 15	86		610	
Jan. 22	34		0	
Jan. 29-31	127		610	
Feb. 6	128		610	
Feb. 12-15	41	85	0	−126
Feb. 19	42		0	
Feb. 23-25	103	285	610	+222
Apr. 15-18	93	137	114	−116

calcium level. Plasma phosphorus levels are not quoted here. They changed in a seemingly haphazard manner, presumably because the dietary content of phosphorus was more variable in the mixed diets than was the calcium content. The calcium balance and urine calcium data are shown on Table 2.

Clinical Changes. The clinical changes in the patient were most interesting to observe and closely followed the changes in the plasma calcium level. On the calcium-free diet he got rapidly better, being more lively and taking his food much more easily. Each time he was given the calcium-containing diet (which invariably produced rises in the plasma calcium level) his condition worsened. He became more fretful and difficult to feed. He was also less active. On the second occasion the calcium-containing diet was maintained for a fortnight instead of a week, as it seemed possible that he would become acclimatized to the higher calcium intake and that our previous result for one week may only have represented a temporary rebound phenomenon. The plasma calcium level continued to rise as fast during the second week on the calcium-containing diet as during the first week, to reach the high level of 15·5 mg./100 ml. A few hours after the child had been put back again on the calcium-free diet he suddenly collapsed in a state of apparently complete hypotonic paralysis, from which he recovered spontaneously after about 20 minutes. An electrocardiogram done soon after did not show changes suggestive of hypokalaemia so we interpreted this collapse as being due to the high plasma calcium level. At all events he rapidly improved in the next few days on a calcium-free diet. It appeared to us that during the course of this illness from the middle of February onwards he was becoming more tolerant of his dietary calcium. It was also of special note that several times during the course of the investigation, he had respiratory infections and febrile attacks whose cause was not always known. These complications only arose while he was taking calcium-containing diets. He was eventually sent home on May 20, 1953, the mother being advised to continue his diet containing about 200 mg. calcium with the high phytic acid content in the form of 'all-bran'. She was also advised to keep him out of the sun as much as possible to avoid the possibility of vitamin D synthesis on the skin.

Follow-up of the Patient

The child was seen at monthly intervals at first; later at three-monthly intervals. He remained on the 'all-bran' and low calcium intake until July 5, 1953. He was doing very well at this time and radiographs showed good growth of bone with no suggestion of rickets. His mother was then advised to add one cup of milk a day to his previous diet so as to raise his intake to about 400 mg. of calcium a day and she was told that from now on she need not worry about exposing him to the sun. On August 7, 1953, he showed further improvement. The plasma calcium level was 10·6, phosphorus 5·5, urea 36. He was told to eat any food he liked from now on with the one restriction that milk should be limited to two cups a day. From December 7, 1953, he was told to drink as much milk as he liked. Occasional attacks of bronchospasm had occurred and on February 20, 1954, he was admitted to St. Margaret's Hospital, Epping, with an attack of bronchitis and asthma. He responded well to ephedrine and sulphadimidine and went home on April 1, 1954. He was in excellent condition on May 31, 1954; appetite good, and his mother said that he was then drinking 1-1¾ pints of milk a day. The plasma calcium level was 9·9, urea 42. He continues well to the time of writing (April, 1955) when the plasma contained (mg./100 ml.) Ca, 10·3; P, 4·6; urea, 24.

Growth charts for weight and length are shown in Fig. 3. It can be seen when comparing his levels with the normal percentiles that he was grossly retarded around the age of 9 months, when this disease began, but that he made spectacular progress later and has now reached the 50 percentile levels of both weight and length. He is now very lively both physically and mentally, and appears well up to normal intelligence.

Discussion

We have described here the investigations and treatment of an infant who seems to fit very well the syndrome described by Lightwood (1952) as idiopathic hypercalcaemia of infancy with failure to thrive. The investigations seem to have shown clearly that this child was abnormally sensitive to vitamin D since, when he was given 10,000 units a day as calciferol for 10 days in the beginning of December, 1952, he deteriorated rapidly and the plasma calcium and urea levels rose. This dose could have no such effect on a normal child, but in view of the known natural history of the disease it could still be argued that the change in the child's condition was spontaneous and not due to the vitamin D given. Investigations while he was in the metabolic ward showed the extraordinary lability of the plasma calcium level and its close dependence

on changes in calcium intake. Clinical observations also showed a close correlation between his state of well-being and the plasma calcium level. At first sight this could be described as an intoxication by calcium since this was the only factor which varied throughout most of the investigation. The data suggest good absorption of calcium from the gut, although unfortunately it was not possible to perform good balance determinations in the earlier periods in which calcium was present in the diet

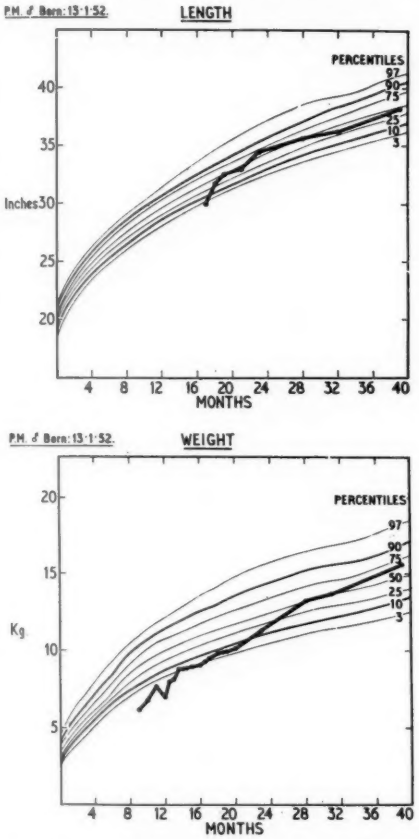

FIG. 3.—Growth and body weight curves during the illness and subsequent two-year follow-up.

owing to the child's poor condition. It can be presumed that there was good absorption from the gut at this time since it is difficult to see how otherwise the plasma calcium level could change so markedly and rapidly with changes only in the intake. This good absorption could be explained either as the continuing result on an exceptionally sensitive infant of the moderate doses of vitamin D given in early December, 1952, or in previous diet, or as due to the disease itself acting on some other still unknown mechanism. However, the former possibility seems more likely since the abnormality of calcium metabolism observed mimics so very closely an overdose of vitamin D in the normal subject. We would stress here the low alkaline phosphatase level which is typically found in vitamin-D intoxication (Fanconi and de Chastonay, 1950) and was present in our infant; it has been reported without comment in some other cases of idiopathic hypercalcaemia. It is interesting to mention here the apparently identical disorder of calcium metabolism which occurs in some cases of sarcoidosis. There is good evidence that this also is due to an abnormal sensitivity to vitamin D (Anderson, Dent, Harper and Philpot, 1954; Henneman, Carroll and Dempsey, 1954). If this theory be accepted as feasible, a logical means of treating the condition appears, for we can argue that most of the symptomatology can be related to the raised level of plasma calcium and to the complications known to follow from this. We must stress that when the plasma calcium has been raised for a long time the renal damage may last for some time after the calcium has returned to normal. In such a case the correlation between plasma calcium level and clinical features will not be as close as we observed in the acute observations in our patient. The aim of the treatment must, therefore, be to lower when necessary the plasma calcium to normal levels. One means of achieving this will be to put the infant, as we have done here, on an intake of calcium tolerable without hypercalcaemia and on a diet which is otherwise quite free of vitamin D. This has already been reported with hopeful results by Russell and Young (1954), by Ferguson and McGowan (1954) and by Macdonald and Stapleton (1955). We should expect that this treatment would have to be continued for some months to use up stores of vitamin D. After this, the calcium intake can be raised but vitamin D should be given only when it is shown that the child can tolerate ordinary doses. It may be that the addition of calcium-complexing agents to the diet will enable a diet effectively free of calcium to be prepared more easily. We attempted this in a preliminary fashion by adding phytic acid (as 'all-bran') to the diet. However, our evidence is not strong enough for us to conclude that this was effective. Clearly the possibility of the development of rickets must be borne in mind in any child kept on low calcium and low vitamin D diets for some time, since the calcium balance will be negative during the treatment (Table 2).

Another obvious method of treatment, and one much more easy to realize in practice, is to give cortisone to the infant while it remains insensitive to vitamin D. This treatment has been most successful in the hypercalcaemic cases of sarcoidosis

where the results obtained have suggested strongly that comparatively small doses of cortisone have an anti-vitamin D action (Anderson *et al.*, 1954). It is interesting that cortisone has already been given for a short trial by Creery and Neill (1954) to one infant with idiopathic hypercalcaemia with apparent benefit, and also by Macdonald and Stapleton (1955).

With regard to the nature of vitamin D intoxication, there has been considerable doubt in the past as to whether pure vitamin D produces toxic symptoms only by virtue of the effects of the hypercalcaemia, or whether some, at least, of the toxicity is due to another action of the vitamin or to other substances present in the vitamin D preparations used. The present study suggests that the intoxication is due mainly at least to the hypercalcaemia, although we have data on other patients indicating that other factors may also be involved and also that the level of hypercalcaemia which produces toxic symptoms varies very greatly from patient to patient. We have known some adults intoxicated with a plasma calcium level of 11·5, while others may be almost symptom-free with a level of 19. In the same patient, however, the same critical level of toxicity seems to remain fairly constant. If the disease processes in our infant did indeed result from a sensitivity to vitamin D, it is clear that in him at least it was mainly the hypercalcaemia which was their immediate cause since all other circumstances were so closely controlled and since repeated alternations of illness and well-being followed changes only of plasma calcium level, induced by changes only in calcium intake.

The main problem remains as to why certain infants may be far more sensitive to vitamin D than others and why they eventually recover spontaneously from this condition. We have no explanation, and can only suggest that the widespread habit of supplementing prepared foods with additional doses of vitamin D may be dangerous as well as seemingly unnecessary. It is of interest to recall that the same point was made for the same reasons by Thatcher in 1936.

Summary

A case of idiopathic hypercalcaemia presenting in a boy of 9 months is described.

He was given for 10 days 10,000 units a day of vitamin D by mouth at a time when the disease was in a state of moderate remission. This was followed by an exacerbation of the disease.

His response to a diet alternately containing no calcium at all and then 610 mg. per day of calcium (all other factors being constant) was then noted. On the calcium-free diet the plasma calcium level returned quickly to normal and he rapidly improved clinically. On the calcium-containing diet the plasma calcium rapidly rose to abnormal levels and he became ill again. He eventually made a spontaneous recovery and became able to tolerate a normal diet. A two-year follow-up has been maintained during which normal growth and development have been observed.

The clinical and metabolic disorders mimicked closely an intoxication with vitamin D. Presumably the patients with this disease are abnormally sensitive to the vitamin, as most of them appear to have taken only moderate doses.

The theoretical basis of treatment should be a low-calcium vitamin D-free diet, or else a normal diet taken with cortisone to antagonize the vitamin D in the diet and body stores.

We wish to thank Sister C. Turner and Sister A. Edwards for their nursing care of the patient; Miss D. Tuck for supervising the diets; Drs. J. Anderson and B. Senior for medical assistance; Mr. G. Philpot and Dr. J. Anderson for biochemical assistance, and Mr. V. K. Asta for drawing the figures.

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PROTEIN CATABOLISM AND RENAL FUNCTION IN THE FIRST TWO DAYS OF LIFE IN PREMATURE INFANTS AND MULTIPLE BIRTHS

BY

R. A. McCANCE and E. M. WIDDOWSON

From the Medical Research Council Department of Experimental Medicine, University of Cambridge

(RECEIVED FOR PUBLICATION JUNE 5, 1955)

It was shown by McCance and Strangeways (1954) and McCance and Widdowson (1954a, b) that the protein breakdown of normal full-term infants amounted to about 79 mg. N/kg. body weight/24 hr. over the first two days of life if the infants were given during this time 50 ml. of water but no food. The comparable figure for healthy adults was 174 mg. N/kg. of body weight/24 hr. It has also been shown by the same investigators that the extent of this tissue destruction may be influenced by the nature of the maternal labour and the infant's delivery.

The composition and volume of the urine and various aspects of renal function in the first two days of life have been studied by Thomson (1944, 1947, 1949), Smith, Yudkin, Young, Minkowski and Cushman (1949), Hansen and Smith (1953) and McCance and Widdowson (1954a, b), and further references may be found in their papers. In brief, it was found by McCance and Widdowson (1954a) that under the conditions described above the volumes of urine passed by healthy newborn infants per kg. of body water were not very different from those passed by adults but that the osmolar concentrations were much lower and so were the glomerular filtration rates and urea clearances. The glomerular filtration rate was not consistently determined, but the endogenous creatinine clearance was measured in six of the babies and it was generally about twice as high as the urea clearance. The urea and creatinine clearances were found to be adversely affected by a prolonged and difficult labour and delivery. The present paper describes an extension of these investigations to smaller babies and multiple births.

Subjects and Methods

Two premature baby boys, four pairs of twin boys and one set of triplets have been studied. In all cases labour had been normal, and records of the mother's age, her health during pregnancy, the degree of prematurity by dates and the babies' weights and progress are given in Table 1. The methods used were the same as those described by McCance and Widdowson (1954a). No blood, however, was withdrawn from the triplets after birth while they were alive. A sample was taken from the heart immediately after death.

Results

Table 2 shows the concentration of urea in the serum of the single babies and twins at birth and after 24 and 48 hours. There are points of general and individual interest. In six out of the 10 babies the concentration fell during the second 24 hours and the average (admittedly influenced by numbers 7 and 8) shows this clearly. Only five out of the 16 normal babies previously studied reduced the concentration of urea in the body fluids during the second 24 hours of their lives, and the average figures, also given in Table 2, reflect this. None of the 'distressed' babies, i.e., babies born after difficult and protracted labours (McCance and Widdowson, 1954b) lowered their serum urea concentration during the second 24 hours *ex utero* and the average for these babies is also given in Table 2. The general conclusion must be that the present series of small babies had kidneys fully as capable of coping with the demands made upon them as those of normal full-term babies. They were certainly in no way 'distressed' in the sense of the term used by McCance and Widdowson (1954b). The third pair of twins, babies 7 and 8, were instructive in this connexion. They were the sons of a mother with hydramnios and oliguria who had had an antepartum haemorrhage, and the concentration of urea in the cord sera was the result of maternal renal

TABLE 1
NOTES ON MOTHERS AND BABIES

No.	Mother			Baby				
					Body Weight (kg.)		Clinical Assessment	
	Age (years)	Health during Pregnancy	Delivery	Gestation (weeks)	Birth	48 hours	At Birth	Progress
1	22	Pre-eclamptic toxaemia	S.V.	34	1·98	1·80	Poor, respiration delayed 10 min.	Slow improvement after 1 hr.
2	21	Mild toxaemia	S.V.	36	1·98	1·85	Blue asphyxia, head bruised	Rapid recovery
3	31	Good	S.V.	38	1·90	1·77	Very good	Normal
4			S.V.	,,	2·16	1·96	,, ,,	,,
5	17	Toxaemia	S.V.	40	2·27	2·00	Foetal distress, head bruised, shocked	Steady improvement
6			S.V.	,,	2·50	2·27	Good	Normal
7	29	Oliguria, hydramnios, A.P.H.	S.B.	35	2·36	2·10	Good	Normal
8			Breech Forceps to head	,,	2·42	2·16	,,	,,
9	35	Toxaemia	S.B.	39	2·36	2·10	Good	Normal
10			Vertex (forceps)	,,	3·10	2·81	,,	,,
11 ♂	28	Good	S.V.	27½	1·08	1·01 (at death)	Blue asphyxia	Long periods of respiratory failure treated with intragastric O_2
12 ♀			S.B.	,,	1·16	1·14 (at death)	,, ,,	
13 ♂			S.B.	,,	1·08	1·05 (at death)	,, ,,	Duration of life (Table 3)

S.V. = Spontaneous vertex. S.B. = Spontaneous breech.

insufficiency. Yet both these infants had excellent renal function as judged both by the changes in the serum urea concentration and by the evidence given below. The first pair of twins, babies 3 and 4, whose mother had had an uneventful pregnancy, had lower concentrations of urea in the cord sera than any of the other children at birth, but their renal function, as indicated by the course of the serum urea concentration, was not so good as it was in some of the infants delivered of toxaemic mothers, who had been born with a higher concentration of urea in the sera, numbers 7 and 8, for example. It appears, therefore, that toxaemia of the mother may impair maternal but not infantile renal function, whereas a prolonged and difficult labour may, temporarily at any rate, impair both (McCance and Widdowson, 1954b).

The triplets, who were scarcely of viable age, all died, and the concentrations of urea found in their sera at death (Table 3) indicate that their kidneys did not excrete the amount of urea liberated into the body fluids. This was, however, in itself large, and defective renal function was probably not the only reason for the height of the serum urea at death. The concentration of potassium at the moment of death was 14·1 mEq./l. in the serum of triplet 1 and 12·5 mEq./l. in the serum of triplet 2. These figures are about three times higher than the normal for an adult, but there is no reason to suppose that high concentrations of potassium were one of the causes of death, since similar ones have been found in cord sera (Kotikoff, 1933). In the fourth pair of twins, for example, the serum K amounted to 13·3 and 12·5 mEq./l. respectively. There are indeed grounds for belief that foetal extracellular fluids may

TABLE 2
CONCENTRATION OF UREA IN SERUM OF SINGLE PREMATURE BABIES AND TWINS

Baby No.	Concentration of Urea in Serum (mg./100 ml.)		
	Cord	24 hours	48 hours
1	27·2	41·0	31·8
2	33·0	49·0	50·0
3	15·5	36·5	59·2
4	14·6	23·5	32·8
5	32·1	44·6	49·3
6	29·7	25·7	18·2
7	81·0	93·6	60·0
8	81·8	80·0	40·6
9	34·0	42·0	35·6
10	33·2	34·0	20·0
Average	38·2	47·0	39·8
Average omitting 7 and 8 ..	27·4	37·0	37·1
Average for 17 full-term normal babies	22·9	33·2	36·0
Average for 9 full-term distressed babies	37·3	62·6	86·2

TABLE 3
CONCENTRATION OF UREA IN THE SERUM OF THE TRIPLETS

Triplet	Concentration of Urea in Serum (mg./100 ml.)		Duration of Life (hours)
	Cord	At Death	
1st	20·6	98·6	45
2nd	20·6	29·4	9
3rd	20·6	75·1	18

TABLE 4

VOLUME AND COMPOSITION OF THE URINE OF SINGLE PREMATURE BABIES, TWINS AND TRIPLETS

Baby No.	Volume (ml./l. body water in 48 hr.)	Composition						
		Total Osmolar Concentration (m. osmols/l.)	Urea (m. osmols/l.)	Cl (mEq./l.)	Na (mEq./l.)	K (mEq./l.)	Total N (mg./100 ml.)	Ratio N : K (mg.)
1	52·0	248	89	27	20	42	354	2·3
2	15·3	400	169	32	30	75	653	2·3
3	7·1	458	123	52	50	70	573	2·2
4	30·8	390	140	80	52	62	634	2·9
5	32·8	475	220	36	40	66	740	3·1
6	38·7	387	137	54	29	68	522	2·1
7	51·3	310	209	15	23	37	614	4·5
8	42·7	337	200	19	33	30	679	6·3
9	14·9	477	262	12	19	41	930	6·1
10	28·3	418	190	44	26	54	688	3·5
Average	31·4	390	174	37	32	55	639	3·5
Average for 18 full-term normal babies ..	27·5	420	157	44	31	46	639	3·5
Average for 10 full-term distressed babies	22·7	419	162	26	27	25	727	10·2
1st triplet	5·2*	312	57	37	64	33	294	2·3
3rd triplet	1·0†	308	39	48	57	18	216	3·3

* ml./l. body water in 45 hr.
† „ „ „ „ 18 hr.

usually contain much higher concentrations of K than would ever be regarded as normal in an adult (Edelstein and Ylppö, 1921; Bakwin and Rivkin, 1927; Green and Macaskill, 1928; Bassadone, 1940).

Table 4 shows the volume of the urine, the total osmolar concentration, the total N, the urea, the chloride, sodium and potassium and the nitrogen/potassium (N/K) ratios. The volumes were very variable, even within the pairs of twins, but the range among the 'thriving' babies was little wider than that previously found among a group of normal full-term infants, and the average was just a little higher. The volumes passed by the two male triplets before they died were very small, and even if the infants had lived to be 48 hours old there is every indication that the volumes of urine likely to have been passed by them up to that time would also have been quite abnormally small. The total osmolar concentrations of the urines passed by the 'thriving' babies were much less variable than the urine volumes and this was also found among the group of normal full-term babies (McCance and Widdowson, 1954a). The explanation then given was that the output of water was essentially being regulated by the rate of excretion of osmotically active material—by osmotic diuresis in other words. It may now be added that variations in the number of functional glomeruli rather than in the reabsorptive activity of the upper parts of the tubules determined the amount of osmolar material being excreted. The present results support the idea of an osmotic diuresis, although a reservation must be made in the case of baby 1, who may have been excreting some 'free' water. The average osmolar concentration for the group of 'thriving' babies was 390 m. osmols/l., just a little lower than that found among the normal full-term babies, and this is in keeping with the fact that their average urine volumes were slightly higher. Although the volumes of urine passed by the two male triplets were very small, the osmolar concentrations were little above the serum level. Their glomerular filtration rates must have been extremely low and their tubules were not concentrating the filtrates, but the evidence available does not indicate whether this was due to their immaturity or to a gradual failure of metabolic functions with the approach of death.

The composition of the urines of the 10 'thriving' babies, as judged either by the amounts of the various constituents present per litre or by their contribution to the total osmolar concentration, differed little from that of normal full-term babies or of 'distressed' babies. The two male triplets, however, had unexpectedly little urea in their urines and a correspondingly large amount of sodium salts. Thus urea accounted for only some 15% of the total osmolar concentration in these urines, whereas the sodium ion contributed about 20%. The N/K ratios were quite normal, i.e., they resembled those of normal full-term infants, but not those of 'distressed' infants or normal adults.

Table 5 gives the amount of nitrogen appearing as end-products, the proportion of this excreted and the urea clearances of the 10 'thriving' babies and of

TABLE 5

NET AMOUNT OF NITROGEN APPEARING AS END-PRODUCTS, PROPORTION EXCRETED AND UREA CLEARANCES

Baby No.	N Appearing as End-products (mg./kg. body wt./24 hr.)	Percentage of N Excreted	Urea Clearance over 48 Hours (ml./42 l. body water/min.)
1	80	97	12·0
2	67	62	5·0
3	99	17	1·9
4	114	73	15·2
5	123	82	14·5
6	55	149	20·5
7	78	167	11·7
8	32	367	14·5
9	53	109	8·3
10	45	163	16·1
Average	75	129 (94 ex. 7 and 8)	12·0
Average for 18 full-term normal babies ..	79	80	11·9
Average for 10 full-term distressed babies	144	39	5·2
1st triplet	178	4	0·71
3rd triplet	271	1	0·014

the two male triplets. The first is the measure of protein catabolism and its average for the 'thriving' premature babies was just below that of normal full-term infants. The average figure for the second was well above 100, as against one of 80 for full-term infants. Figures much above 100 in this connexion result from falling concentrations of urea in the body fluids, and indicate as a rule high urea clearances, coupled with a low protein catabolism. This combination was reinforced in the third pair of twins by the high concentration of urea in the body fluids at birth, but even if they are excluded the average is still above that for full-term infants. The urea clearances averaged 12 ml./42 l. of body fluids/24 hr., and the normal full-term infants had clearances which averaged just under 12 ml./42 l. of body fluids/24 hr. The endogenous creatinine clearances of six of the premature babies, like those of the full-term babies, were about twice as high as the urea clearances. As in the normal full-term babies, moreover, the clearances of the 10 'thriving' babies tended to rise in the second 24 hours of their lives. There is a distinct suggestion in these results that the tissue breakdown was greater and the urea clearance lower in the first twin to be born. This will require confirmation on larger numbers, but some such result as this would not be unexpected in the light of the abnormally high protein breakdown and low urea clearances frequently exhibited by infants who have been subjected to a prolonged and difficult labour. It would not have been surprising if infants with this degree of prematurity had been found to have had appreciably lower urea clearances than those of full-term babies and the present results ought to be reassuring to those responsible for the care of premature infants.

The two male triplets had a high protein catabolism. Without thriving controls of the same size it is impossible to say whether these were pathological or not, although it is highly probable from the clinical behaviour of these babies that they were. Only one of them, however, broke down appreciably more body protein than the average value for a normal adult and, since a human infant weighing only 1 kg. must have next to no fat in its body, the total metabolism of these infants must have been very low unless they were born with very large stores of glycogen. The percentage of nitrogenous end-products appearing in the urine of these two infants was trifling and their urea clearances exceedingly low. They were pathologically so, moreover, for whereas triplet A had a clearance of 2·4 ml./42 l. body water/min. for the first four hours of its life, his clearance later fell to 0·023 ml. as he deteriorated clinically.

Table 6 gives the concentration of inorganic P found in maternal serum and cord serum, and the total amounts of P excreted on the first and second days of life. These results must be regarded as quite normal. They closely resemble those found in normal full-term infants and not those sometimes found in distressed babies (McCance and Widdowson, 1954a, b, c). The rise in the output of P on the second day is usual, but very variable and, as has been stated before (McCance and Widdowson, 1954a), cannot be related to changes in the plasma. Baby 6, for example, had a serum P of 7·9 mg./100 ml. at birth and one of 7·75 mg./100 ml. at the end of 48 hours, yet he excreted 3·6 mg. in the first 24 hours of his life and 22·7 in the second.

TABLE 6

INORGANIC PHOSPHORUS IN SERUM AND PHOSPHORUS EXCRETION

Baby No.	Concentration of Inorganic P in Serum (mg./100 ml.)		Baby's P Excretion (mg./kg. body wt./24 hr.)	
	Mother	Cord	Day 1	Day 2
1	4·30	6·40	2·34	18·00
2	4·65	6·60	0·07	1·07
3	3·00	6·00	0·02	2·95
4	"	4·45	0·14	7·75
5	5·35	7·05	2·46	16·20
6	"	7·90	1·44	10·00
7	4·25	6·45	0·12	5·70
8	"	5·30	6·08	6·48
9	4·25	7·15	0·16	1·97
10	"	6·25	0·00	0·42

Discussion

The renal function of the 10 'thriving' premature babies differed so little from those of normal full-term infants that there is really nothing to add to the discussion in the previous paper (McCance and Widdowson, 1954a). Where comparable, the results agree with those of Hansen and Smith (1953). Perhaps the most interesting findings have been (1) the strictly 'normal' amounts of nitrogen which have appeared as end-products, normal in this connexion being taken as the 'usual' for a full-term baby. This must be the result of a very low tissue breakdown in spite of the absence of food and a relatively small store of fat. The biochemical background of this has been discussed (McCance and Strangeways, 1954), but is not yet known. (2) The absence of any of the signs of 'distress' to be expected after a prolonged and difficult labour: this is a satisfactory finding since, although two of the babies were assisted into the world by forceps, these small babies were born without delay or difficulty. (3) The lack of any necessary association between the maternal renal function, as judged by the state of the mother or the concentration of urea in cord blood, and the renal function of the infants after birth.

Summary

Over the first 48 hours of their lives, and in the absence of all food and of sufficient water to maintain full hydration, twins and premature infants exhibited (*a*) a tissue breakdown which resembled that of normal full-term infants and (*b*) renal functions fully as capable, if not more capable, of providing a normal *milieu intérieur*.

Two of a set of scarcely viable triplets, each weighing about 1 kg., showed signs of abnormally high protein catabolism and defective renal function before they died, but without thriving controls of the same size it is impossible to analyse these results.

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PROGERIA AND ATHEROSCLEROSIS

BY

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The term 'progeria' was first used by Gilford in 1902 to describe a condition of premature senility occurring in children, although Hutchinson had reported the first case in 1886 under the title of 'Congenital Absence of the Hair and Mammary Glands'. The fully developed picture is one of retarded development combined with premature old age, the child rapidly becoming an old, wizened dwarf. Death occurs most commonly in the second decade. Both sexes are affected and there is no familial tendency. The aetiology of progeria remains obscure, although the anterior pituitary gland has been implicated by some authors. Thomson and Forfar (1950) reviewed the literature and found 18 typical and an equal number of atypical cases which did not show the complete picture. They described a case of their own and since then five further cases have been reported (Rossi, 1951; Cooke, 1953; Doub, 1953; Atkins, 1954; Plunkett, Sawtelle and Hamblen, 1954).

A further case of progeria is described. In this child, who was only temporarily resident in the area, some of the endocrine functions have been assessed and a study has been made of the circulating lipid and lipoprotein patterns.

Case Report

P.M. was 3 years old when referred to the Royal Hospital for Sick Children, Edinburgh, because of baldness. He is the third child of healthy, unrelated parents and was delivered spontaneously one month before the expected date, after a normal, uneventful pregnancy. His birth weight was 2·86 kg. (6 lb. 5 oz.). Breast feeding was successfully established and maintained for five months.

He gained weight normally for about six months, but thereafter his weight gain became progressively slower, although he never lost weight. From the age of about 4 months his mother noticed that he tended to be blue about the lips. He sat at 7 months, crawled at 11 months, walked at 15 months and the first tooth was cut at 1 year. Speech developed normally during the second year and he has always been intelligent and in some ways precocious. His appetite has been variable, but on the whole he eats less than other children. He sleeps with his eyes partly open. During the second year his hair, which had grown normally until then, became thinner and the scalp veins were more prominent. Apart from an acute respiratory infection when 2 years old he has been well and has had none of the infectious diseases; he has never played much with other children, but is in no way distressed by exertion.

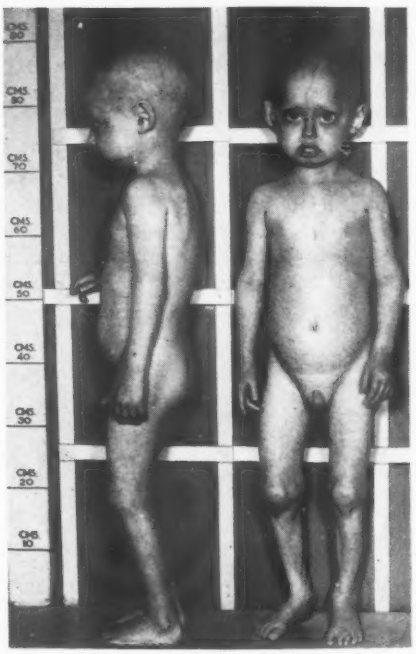

FIG. 1.—The characteristic facies and 'horse-riding' stance.

His parents are well developed physically. The first child of their marriage died at 6 months of age from 'congenital heart disease', but a post-mortem examination was not carried out. The second and fourth children, now aged 5 years and 1 year, are well and normally developed.

When examined at the age of 3 years, P.M. presented the characteristic picture of progeria (Figs. 1 and 2). His measurements are presented in Table 1. He was a friendly little fellow and showed a keen interest in his

TABLE 1

MEASUREMENTS OF PRESENT CASE COMPARED WITH THE AVERAGE FOR A BOY OF 3 YEARS

	P.M.	Average
Weight (kg.)	10·3 (22 lb. 11 oz.)	15
Height (cm.)	88·7 (34⅝ in.)	92
Circumference (cm.) of		
Head	47·7 (18¾ in.)	50
Chest	46·0 (18⅛ in.)	52
Abdomen	47·0 (18½ in.)	47
Arm span (cm.)	82·0 (32¼ in.)	
Pubis to feet (cm.) ..	36·4 (14⅜ in.)	
Umbilicus to feet (cm.) ..	46·0 (18⅛ in.)	

surroundings, ready to copy any new actions he saw and asking questions constantly. His voice was rather high-pitched and at times difficult to follow, but his vocabulary was good and his power of conversation advanced for his age. He was happiest when occupied, particularly with mechanical toys, and did not appear unduly irascible. He could run quite well, but preferred to walk slowly. Sometimes, instead of joining in games with other children, he stood by watching with an aloof,

FIG. 2.—The scanty hair, the abnormal ears and the pigmentation of the skin.

superior demeanour. When standing, there were frequent restless movements of the hands and wrists with a rocking movement from one foot to the other. Incomplete extension of the hip and knee joints together with failure of full extension of the elbow gave the typical 'horse-riding' stance.

The skin generally was dry and lacked the normal elasticity, and there was little or no subcutaneous fat except over the abdomen and in the cheeks. There were no cutaneous xanthomatous lesions, but a reticulated brown pigmentation was present over the trunk and neck

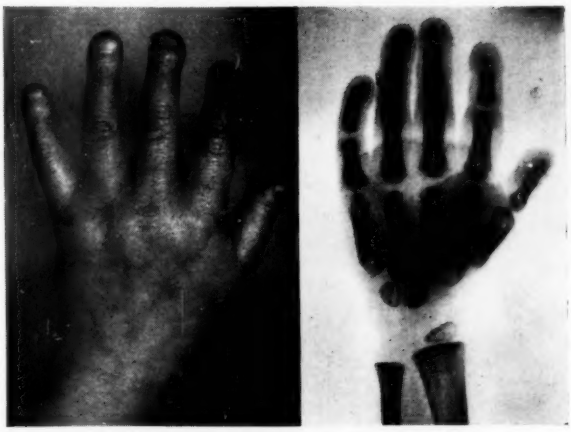

FIG. 3.—Hypoplasia of the terminal phalanges.

and there were some freckles on the face (Fig. 2). The nipples were not abnormal.

The scalp had only a few wispy hairs. The skull appeared large in relation to the face, and the anterior fontanelle and sutures were not closed; a continuous souffle was heard on auscultation in both temporal areas. There were no eyebrows and only scanty eyelashes; the eyes were large and prominent and there was no arcus senilis and no epicanthic fold. The nose was narrow at the bridge and generally thin, yet in contrast the cheeks were relatively plump. The lips were normal, but the surrounding skin had a bluish tinge not observed elsewhere. The mandible was poorly developed and there was a large dimple at the point of the chin; there were 16 teeth which were in good condition and not unduly crowded. The ears were prominent with a large external meatus and poorly formed lobules.

The limbs were thin, bringing the joints, particularly the knees, into prominence. The nails were complete but short in relation to their breadth, the whole terminal phalanx being poorly developed (Fig. 3). The thorax had a narrow inlet but the clavicles were palpable. The heart sounds were normal and no murmurs were heard. Blood pressure was 110/64 mm. Hg. There was no palpable abnormality of the peripheral arteries and the retinal vessels appeared normal on ophthalmoscopy.

The abdomen was prominent and the overlying skin felt abnormally firm. It was not possible to palpate the liver, spleen or kidneys. The external genitalia were normal for a boy of his age and both testicles were in the scrotum. Physical examination of the respiratory and central nervous systems showed no abnormality. There were no palpable glands.

Radiology. In the skull (Fig. 4) there was no abnormality of the sella turcica. Slight gaping of the posterior sutures was observed with sutural bone formation in the posterior coronal and right lambdoidal sutures. There was moderate hypoplasia of the maxillae and marked hypoplasia of the mandible both in the horizontal and ascending rami; the second deciduous molars were unerupted.

Both clavicles were attenuated, tapering off at the extremities. Metaphyseal angulation of the proximal

FIG. 4.—A normal sella turcica, an open fontanelle and open lambdoidal sutures.

ends of the radii was present and there was hypoplasia of the terminal phalanges of both hands (Fig. 3).

The lumbosacral spine was bifid. There was marked coxa valga with bowing of the femora (Fig. 5). Moderate generalized osteoporosis was noted, the ossification

FIG. 5.—The coxa valga and bowing of the femora.

generally being average for the age. There was no pulmonary lesion but slight generalized enlargement of the heart.

Electrocardiography. Electrocardiography showed sinus arrhythmia, and a heart rate 107 per minute; the PR interval was 0·10 sec. The standard, unipolar limb and six V chest leads were normal before and after exercise.

Urine. Specific gravity was 1,030 maximum and 1,003 minimum. No albumin or reducing substance was present. The total amino-acid nitrogen content was 27·4 mg. %. A one-way chromatogram was normal. Creatine excretion per 24 hours was 101 mg., and creatinine per 24 hours, 143 mg.

Blood. Haemoglobin was 10·65 g. %, red blood cells, 4 m./c.mm. The P.C.V. was 36·0 mm. The urea nitrogen level was 8 mg. %. The serum creatinine level was 0·3 mg. %, serum sodium, 316 mg. %, serum chlorides, 582 mg. %, serum potassium, 23·4 mg. %. The serum CO_2-combining power was 57 vol. %. The serum calcium level was 10·9 mg. %, the serum inorganic phosphorus, 5·0 mg. %, the serum alkaline phosphatase, 14 King-Armstrong units. Serum proteins totalled 7·4 g. % (albumin, 5·4 g. %, globulin, 2 g. %).

Circulating Lipids and Lipoproteins. These are given in Table 2.

TABLE 2

CIRCULATING LIPIDS AND LIPOPROTEINS

	Patient	Means of Normal 3-year-old Children
Plasma total cholesterol (mg. %) (Sperry and Webb, 1950) ..	225–240 (Average 230)	149
Plasma total cholesterol : phospholipid ratio (C/P ratio) .. (lipid phosphorus by the method of Allen, 1940)	0·99–1·30 (Average 1·07)	0·74
Concentration of cholesterol attached to the alpha lipoprotein fraction expressed as a ratio to that attached to the beta lipoprotein fraction (Boyd, 1954)	11 : 89	30 : 70

Endocrine Function Tests. The ratio of day to night excretion of urine and the water test according to the criteria for children of Talbot, Sobel, McArthur and Crawford (1952) were both normal.

Eosinophils numbered 208/c.mm., and four hours after 15 mg. A.C.T.H. intramuscularly, 34/c.mm. Urinary 17-ketosteroids were 0·62 mg./24 hours and 0·87 mg./24 hours. Free formaldehydogenic steroids were 0·145 and 0·095 mg./m² (Lloyd and Lobotsky, 1950).

GLUCOSE TOLERANCE TEST. This test after 20 g. of glucose gave a fasting level of 93 mg. %, at half an hour, 129 g., at one hour, 126 mg. %, at one and a half hours, 107 mg. %, at two hours, 102 mg. %. No glycosuria was noted during the test.

RADIO-ACTIVE IODINE TEST. After 10 microcuries the following results were obtained:

0- 8 hour excretion	43·4%
8-24 hour excretion	12·7%
24-48 hour excretion	2·3%
0-48 hour excretion	58·4%

T. index = 7·8%. Gland uptake after 24 hours = 25%.

TABLE 3
CASES OF PROGERIA WHOSE AGE AT THE TIME OF DEATH IS KNOWN

No.	Authors and Dates Published	Sex	Evidence of Atheroma or Coronary Artery Disease			Age at Death (in years)
			Clinical	E.C.G.	Necropsy	
1	Hutchinson (1886) Gilford (1897)	M	Angina of effort, death from 'syncope'	Not reported	Not done	17
2	Gilford (1897)	M	Choking sensation on exertion	Not reported	Atheroma; both coronary arteries occluded	18
3	Variot (1921) Variot and Pironneau (1910)	F	No clinical history available following description of child at 15 years			22
4	Schippers (1916) Manschot (1950)	M	Nocturnal dyspnoea	Positive	Atheroma, coronary occlusion	27
5	Orrico and Strada (1927)	M	Hemiplegia at 19 years, sudden death	Not reported	Widespread atheroma	21
6	Curtin and Kotzen (1929)	F	Angina, died from coronary thrombosis	Negative at an early age	Not done	9
7	Talbot *et al.* (1945)	M	Angina of effort	Normal at 6 years	Generalized atheroma, myocardial infarcts	7
8	Schwartz and Cooke (1945) Cooke (1953)	M	Angina of effort	Positive	Not done	8
9	Cooke (1953)	F	Angina of effort	Not reported	Not done	13
10	Atkins (1954)	M	Nocturnal dyspnoea, myocardial infarct	Positive	Atheroma, myocardial infarct	11

Biopsy of Skin from Abdominal Wall. The epidermis was normal apart from wrinkling. The pigmentation was by melanin in the basal cells of the epidermis; it was unequally distributed and definitely in excess in some areas. There was no flattening of the interpapillary ridges. Elastic tissue was rather more plentiful and in coarser fibres in the dermis than in a control of the same age. The arrectores pilorum muscles were large and conspicuous, although hair follicles were scanty. There was no evidence of scleroderma or of senile elastosis.

Discussion

One of the most extraordinary features of progeria is the early development of atherosclerosis, the occurrence of which during the first two decades of life must always warrant serious consideration. Of the 24 reported cases of progeria the age of death is known in 10 (Table 3). In five of these the results of necropsy have been published and all have shown evidence of widespread and advanced atherosclerosis and in four occlusions of the coronary arteries and myocardial infarcts were demonstrated. Moreover, of the five cases on which necropsies were not performed, four are recorded as experiencing angina pectoris, in one of which an electrocardiogram suggested myocardial infarction. No details are available concerning the last seven years of life of the remaining case (Variot and Pironneau, 1910; Variot, 1921). The earliest age at which any clinical manifestations of coronary sclerosis have been reported in a case of progeria is 7 years (Talbot, Butler, Pratt, MacLachlan and Tannheimer, 1945).

There is now little doubt that in the adult coronary sclerosis is associated with a disturbance of lipid metabolism and that this disturbance is reflected by abnormalities in the circulating lipids and lipoproteins (Gertler, Garn and Lerman, 1950; Russ, Eder and Barr, 1951; Steiner, Kendall and Mathers, 1952; Oliver and Boyd, 1953, 1955). Cholesterol measurements have been recorded in seven cases of progeria; these measurements, together with any clinical or post-mortem evidence of atherosclerosis, are shown in Table 4. There is no indication in most of these reports of the methods of estimation which were employed or the normal range of the laboratories concerned. In the present case a more complete analysis of the circulating lipids and lipoproteins has been possible (Table 2). The plasma total cholesterol level is elevated above the normal range determined in the same laboratory, but more significant is the elevation of the ratio of

TABLE 4
CHOLESTEROL LEVELS IN CASES OF PROGERIA

Authors and Date	Age of Patient (in years)	Cholesterol (mg./100 ml.)	Evidence of Atherosclerosis
Exchaquet (1935)	14	270	Not reported
Zeder (1940)	5	327	Not reported
Talbot *et al.* (1945)	6	170–300	Atheroma at necropsy
Thomson and Forfar (1950)	4	275	None clinically
Rossi (1951)	3	294	Not reported
Atkins (1954)	3–11	240–287	Atheroma at necropsy
Plunkett *et al.* (1954)	4–17	218	None clinically

total cholesterol to total circulating phospholipids (the C/P ratio) and the abnormally high concentration of cholesterol on the beta-lipoprotein fraction. Such a combination of abnormalities is most uncommon in the adult in the absence of overt coronary sclerosis, xanthomatosis, essential hyperlipaemia, or myxoedema, and presumably very rare at the age of 3. It is interesting that Mitchell and Goltman (1940) report and reproduce a photograph of a cutaneous xanthomatous plaque in a child with progeria aged 10 years.

The genesis of progeria has frequently been related to endocrine dysfunction. It is known that many hormones influence the circulating lipids and lipoproteins, and the demonstration of an abnormal lipid and lipoprotein pattern in the early years of a patient with progeria is not necessarily inconsistent with an elusive endocrine disorder. However, the results of the series of tests undertaken in this child suggest that he is not suffering from any gross upset of endocrine function.

That progeria and atherosclerosis are closely associated would appear evident from the records of previous cases. The abnormal circulating lipid and lipoprotein pattern in this 3-year-old child might possibly be regarded as circumstantial evidence for the presence of coronary sclerosis despite the absence of supporting clinical manifestations. The premature development of atherosclerosis in progeria may possibly be similar in character to its development in the adult, except that the metabolic errors are perhaps inborn in the former and acquired in the latter. By the study of the rapid development of atherosclerosis in the rare cases of progeria, it is possible that further information may be forthcoming to those concerned with its pathogenesis in adults.

Interest in possible pituitary dysfunction has tended to overshadow the presence of atherosclerosis in investigations into the aetiology of progeria. Variot and Pironneau (1910), however, impressed by the report of atherosclerosis in the necropsy on Gilford's case (Gilford, 1897), suggested that it might play an important role in the pathogenesis of this condition. It is tempting to support this view, but at present the aetiology of progeria must remain obscure.

Summary

The clinical features of progeria in a boy of 3 years are described. No evidence of endocrine dysfunction was detected. The pattern of the circulating lipids and lipoproteins was similar to that of an adult with overt coronary sclerosis. The relationship between progeria and the premature development of atherosclerosis is discussed. It is suggested that further study of this association might be rewarding.

We should like to thank Dr. D. N. Nicholson for permission to publish this case, which was under his care, and for his help in the preparation of the paper.

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A FOLLOW-UP STUDY OF 110 PATIENTS TREATED FOR PURULENT MENINGITIS

BY

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As modern therapy has undoubtedly changed the course and prognosis of purulent meningitis, this study was undertaken in order to review the course of our cases and to gain an impression of the ultimate results. For the immediate result all the notes on patients treated in the period from October, 1949, to March, 1954, were scrutinized. In addition, all the patients of this period who survived were checked regarding their physical and mental development at least six months after discharge from hospital. The children were tested according to the directions of Gesell and Amatruda outlined in their book on developmental diagnosis and by the method of Binet-Simon. In addition the behaviour of the child in his surroundings was taken into account, and his development before his illness. For example, when a mongolian idiot developed in a similar fashion after meningitis as before his illness, he was marked as undisturbed.

In the period concerned 114 patients with purulent meningitis were admitted to the Juliana Kinderziekenhuis. Of these patients the aetiological diagnosis was made by direct examination and culture of the cerebrospinal fluid.

When an operation was performed on the mastoids a culture of the pus was made as well. In cases showing the syndrome of Waterhouse Friedrichsen a direct smear was made from the petechiae. By these methods a definitive bacteriological agent was found in 99 cases; in the remaining 15 patients the aetiology was not clear.

Apart from the cases of influenzal meningitis the treatment was much the same in all cases: penicillin, 3-hourly 20-50,000 units, and sulphadiazine, daily 100-200 mg./kg. body weight. In addition, 10,000 units of penicillin diluted in 10 ml. saline were given in some cases intrathecally, mainly at the end of the diagnostic puncture and sometimes for the first few days afterwards as well. In the cases of *H. influenzae* meningitis, the therapeutic scheme divides into two periods. In the first period, until 1951, patients were treated with penicillin three-hourly 20-50,000 units, streptomycin 40 mg./kg. body weight, and sulphadiazine 100-200 mg./kg. In addition, a number of these patients had one or more intrathecal injections of penicillin and/or streptomycin, 1/10-1/15 of the daily dosage. Then chloramphenicol became available, and patients admitted in 1951 and later were treated with a combination of chloramphenicol, 125 mg./kg., and sulphadiazine, 100-200 mg./kg., as soon as they had stopped vomiting.

Of the total of 114 patients, 10 died, including two deaths in children after they had recovered from meningitis. One of these children died from a haemorrhagic diathesis for which he had been admitted on several other occasions. The other child, suffering from a transposition of the great vessels, died six months after meningitis. As it was not possible to give a definite judgment on possible late effects of the meningitis, these patients are not recorded. For the same reason two out of 104 surviving patients are not included in this survey as they did not appear for our routine examination.

Although our results do not look bad at first sight, as only eight patients out of 110 died, the final results are depressing. Of the 102 surviving patients, 16 presented defects, more or less interfering with normal life and development.

When comparing the notes of the patients who still suffer from the sequelae of the 'cured' meningitis, attention is drawn to a certain similarity in the condition of some of them during the acute illness. They were ill several days before admission. On admission symptoms of a focal brain process were manifest. They had convulsions in one arm or one leg or one side of the face. Often they turned head and eyes to one side. They often remained comatose for some days. They had a strange, wild gaze. If there had not been neck rigidity, and sometimes a bulging fontanelle, undoubtedly the diagnosis would have been stated as encephalitis. The following case is an instance.

Case 94. A baby of 7 months, who had had a cold 14 days previously, became ill again one day before

admission. He was drowsy, refused food and then had a convulsion, with contractions in the left arm. On admission he was comatose and had a convulsion involving the right arm and right side of the face. The following two days the condition remained unchanged. The right arm was stretched spastically with the fingers clenched round the thumb and occasionally contracted. In the next few days the condition seemed to improve. The child took his feeds, had no convulsions, the cerebrospinal fluid cleared and the temperature became normal. As the right arm and leg still remained spastic the child was referred to a neurosurgical clinic (the Ursulakliniek) where the E.E.G. showed disturbances on the left side, parieto-occipito-temporal. Trepanation was performed, but there was no hygroma.

In the follow-up study the child appeared to be mentally retarded (I.Q. 60), he had a paresis of the right arm and leg, and was suffering from salaam convulsions.

Case 108. A baby of 7 months, who had been ill for eight days before admission, had had convulsions on the first day. He was rigid, had a squint and, notwithstanding therapy, convulsions started again after two days. The left arm and leg were spastic and the head and eyes continually turned to the left. An operation on the mastoids did not give any improvement. His left arm and leg were moving continuously, and the right arm and leg seemed to be paralytic and showed higher reflexes. Although the cerebrospinal fluid cleared, this child too was transferred to the Ursulakliniek in order to exclude an abscess or hygroma. No fluid was found. The E.E.G. showed an independence in activity of the left and right hemispheres probably caused by a derangement of the brain-stem. Encephalography showed abnormal dilated ventricles, especially on the left side. The end-result is rather tragic: the child is a hopeless mental defective with an I.Q. of 30; convulsions are controlled by 'luminal' and diphantoin, but now and again an akinetic equivalent interrupts his activities. The right arm is spastic.

Both these children were suffering from *H. influenzae* meningitis, both had penicillin, streptomycin and sulphadiazine initially, followed by a course of chloramphenicol and sulphadiazine after two days. The first child (No. 94) had an initial injection of penicillin intrathecally, the other had no penicillin intrathecally. In both cases the results are equally poor and probably due to a meningo-encephalitis.

In our series of *H. influenzae* meningococcal and pneumococcal meningitis we find equivalent examples of this kind as might be shown in the survey. In one case the disturbances are severe, in another there is less interference with the mental development. And a very few cases, which showed initially severe damage and definite signs of meningo-encephalitis, were found to be quite normal after-afterwards. For instance:

Case 109. When aged 18 months this child was admitted to the hospital for a very acute illness. He showed the syndrome of Waterhouse Friedrichsen; he was shocked and the body was covered by petechiae. On his left cheek was a blister raised by burning, from which meningococci were cultured. With an intravenous drip of 'macrodex', noradrenalin and cortisone he recovered from the shock, but still remained unconscious, his head turned towards the right side. Three days afterwards he seemed to react a little. After some days it was obvious that he did not see; there was no reaction at all to moving subjects unless they made a noise as well. The pupils contracted normally when stimulated by light. After 23 days he recovered his perception for light and imitated the nurse when putting out her tongue. No damage could be found afterwards. Most probably the original lesion was localized in the calcarine area. Perhaps there was a little bleeding with a minimal destruction, but at the time of onset a larger area of irritation causing functional defect.

An equally surprising good result was obtained in a very bad case of pneumococcal meningitis.

When, in the following survey, the condition of the patient is stated as a remnant of meningo-encephalitis, the clinical course during the acute illness has been much the same as in the above-mentioned cases.

Fig. 1 relates the distribution of the different types of meningitis to the age of the patients. As can be seen from Fig. 1, pneumococcal meningitis in particular gives rather poor results: of 24 cases, there were three of meningo-encephalitis leading to a child with convulsions and I.Q. of 50%, to a child with ataxia of the right hand and I.Q. of 70%, and to a child with a spastic right leg and arm and I.Q. of 40%, respectively. In addition, another five cases were found to have the following defects: one child with a paretic right foot, one deaf and dumb child, one hydrocephalic child (she died two years after discharge from hospital), one child with aphasia and one child with an I.Q. of 70. The only child who died had been in hospital for 36 hours. On eight of these 24 patients an operation on the mastoids had been performed.

Regarding the 38 cases of meningococcal meningitis, we might conclude that here the danger is in the very acuteness of the disease, especially in the cases with the Waterhouse-Friedrichsen syndrome. Too often no proper chance is left for treatment once the patients enter hospital. The five fatal cases died three, six, eight, 12 and 24 hours after their arrival. It may be stressed here that full attention should be given to anti-shock therapy: we use an intravenous drip of 'macrodex' with cortisone and noradrenalin. Of the cases showing defects, two had had

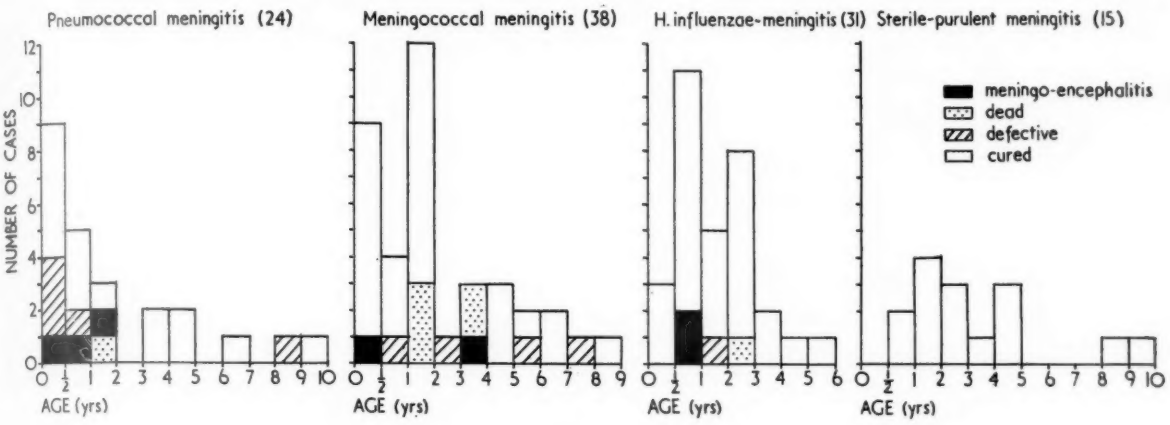

FIG. 1.

meningo-encephalitis: one child now has convulsions and an I.Q. of 30, one child had an aphasia and partial deafness on the right and total on the left side, while of the other three children with defects, one child is suffering from an alexia, one from alexia and agraphia and one has convulsions.

Considering the cases of *H. influenzae* meningitis, we find here the two distressing cases described previously. The one fatal case expired 15 minutes after admission. In *H. influenzae* meningitis chloramphenicol combined with sulphadiazine seems to be superior to a combination of penicillin, streptomycin and sulphadiazine. Since chloramphenicol was introduced no relapses occurred, and the average time in which the C.S.F. cleared to less than 30 cells per c.mm. was remarkably shorter, 16 days; before chloramphenicol was used the average was 25 days and in addition three cases had relapsed.

In our series of sterile purulent meningitis the results have been excellent: none died and not one child shows sequelae.

There has been one case of streptococcal meningitis in a baby of 1 month who died after 10 hours, and one case of *Bact. coli* meningitis in a baby of 10 days. This child is now deaf and also suffers from a congenital dislocation of the hip.

We now wonder if we could expect an improvement in the results from a change in the therapy. Perhaps it would be advisable to give a higher dosage of penicillin, especially in the cases with meningo-encephalitis, where the outlook is worse than in meningitis. It does not need to be stressed that in any case of meningitis at least two antibacterial agents should be used in order to prevent the development of resistant strains.

There still seems to be one point of discussion regarding the use of medication intrathecally. Some authors advise against this method as they think the intrathecal injection may be the cause of the resulting defects. In order to find out whether our cases permit us to come to a conclusion, we have divided them into two categories, with and without intrathecal therapy.

After subtracting the four cases of meningococcal and the one case of influenzal meningitis dying within 12 hours, the final results were 54 cases with intrathecal penicillin (46 good, eight damaged, no death), 51 cases without intrathecal penicillin (41 good, seven damaged, three deaths).

From these figures we cannot state that penicillin, when used intrathecally, is injurious, neither is it possible to state that it is advantageous. However, when considering again the 110 cases, no example could be found where any complications occurred directly connected with an intrathecal injection. On the other hand two cases did show a marked improvement after some days as soon as penicillin was used intrathecally. In these two cases initially no penicillin was given intrathecally. According to the investigations of Dowling, Sweet, Robinson, Zellers and Hirsch (1949) a concentration of 0·05-1·25 units of penicillin ml. was reached in the C.S.F. after only eight hours, even when penicillin was given intravenously in the extremely high dosage of 1,000,000 units two-hourly. According to Alexander, Flippin and Eisenberg (1953), the pneumococci show a delayed growth in a concentration of the penicillin of 0·03 units per ml., so one can only expect any effect from penicillin injected intravenously after eight hours. By giving the penicillin intrathecally one might be able to reduce this delay.

Although in those cases with focal symptoms we looked for a brain abscess of an accumulation of subdural fluid, we found none.

There is one point which should be stressed

TABLE

Type	Intrathecal Medication				No Intrathecal Medication		
	Death	Damaged	Improved after Intrathecal Penicillin	Good	Death	Damaged	Good
Meningococcal ..	1	1 alexia 1 meningo-encephalitis (convulsions + I.Q. 50%)		11	4	1 alexia 1 convulsions 1 meningo-encephalitis (aphasia)	17
Influenzal	0	1 meningo-encephalitis (No. 108) 1 partial deafness		16	1	1 meningo-encephalitis	11
Pneumococcal ..	0	2 meningo-encephalitis (1 ataxia R. hand + I.Q. 70%; 1 convulsions + I.Q. 50%) 1 hydrocephalus 1 3 attacks of meningitis since trauma skull	1 aphasia 1 paretic R. foot	5	1	1 meningo-encephalitis (spastic R. leg + arm + I.Q. 40%) 1 deaf and dumb	10
Sterile	0	0		12	0	0	3
Coliform						1 deaf and dumb	
Streptococcal ..					1		
Total	1	8	2	44	7	7	41

regarding the sequelae which can occur sometimes after a 'cured' meningitis. It seems to be our duty to review these children later on to see whether we still might be able to improve their condition. In some cases we might advise speech therapy, other children should be referred to a deaf and dumb asylum, and in spastic children massage can improve their condition.

Summary

A follow-up study is presented of cases treated for purulent meningitis in the period from October, 1949, to March, 1954. The suggestion is made that in some cases, where from the onset symptoms of a focal irritation of the brain were present and no abscess or accumulation of subdural fluid could be found, a meningo-encephalitis rather than a meningitis alone had led to the residual defects. The prognosis is worse in these cases. Initial intrathecal injection of penicillin is advised, in addition to the treatment with two antibacterial agents.

In cases with *H. influenzae* a combination of chloramphenicol and sulphadiazine gave very good results. All cases of purulent meningitis should be reviewed in a follow-up study.

I am indebted to Dr. W. K. Dicke for his advice and encouragement.

Our sincere thanks are due to Dr. N. P. M. v. Wayenburg and Dr. O. Magnus for their kind cooperation in studying these complicated cases with us and giving us all the data of the patients once the treatment was taken over by the Ursulakliniek.

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ORAL FACTORS IN ACCIDENTAL POISONING

BY

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Perverted appetite as a contributory cause of poisoning has previously excited comment but largely in connexion with poisoning by lead (Burrows, Rendle-Short and Hanna, 1951). Evidence of pica appears, usually without comment, in the cases of other poisoned children. For example, Davis and Hunt (1949) were unable to carry out successful gastric lavage on a child poisoned by an antihistamine as the stomach contained a heterogeneous mass of vegetable matter, and Prain (1950) found a plastic toy in the caecum of another poisoned child. However, exaggerated oral tendencies may not go as far as pica, and the present paper considers the degrees of oral abnormality to be found in children who have poisoned themselves.

Material and Method

The study is based on the histories of 31 consecutive cases of reputed poisoning seen by the writer at a children's hospital. Six of the cases have been excluded from the present series. Of these, one had been given poison in error by his parents, one poisoned himself while on holiday so that an adequate history could not be taken, and a history was not taken in another who was the child of a colleague. The remaining three, acting in concert, ate laburnum seeds. Their average age was over 5 years. Craig and Fraser (1953) pointed out that the average age of 15 children who ate laburnum seeds was $5\frac{3}{4}$ years, whereas the average age of 500 children poisoned by all causes was under $2\frac{3}{4}$ years. This great disparity in the age-groups suggests that the aetiology of laburnum poisoning differs from the aetiology of poisoning as a whole, and the laburnum cases have therefore been excluded from the present series. The remaining 25 cases represent the common poisoning pattern, both as regards age (average, 33 months) and the type of poison taken.

The mother was questioned when the child was about to leave hospital, the time when she was least likely to be confused or over-emotional. It is admitted that, when a mother was asked if her child had a tendency to put things in his mouth, she might have replied 'Yes' to show the poisoning as inevitable. On the other hand, it could be argued that she would reply 'No' to excuse her own lack of foresight in not keeping a poison from him. In practice, it was found that the mother replied promptly and did not seem to consider the significance of the questions before replying. It is believed that the case histories are valid.

As oral tendencies are common in the child population, an 'oral history' was taken from 25 controls. These were children aged from $1\frac{1}{2}$ to 4 years (average, 31 months). They attended, or were siblings of those who attended, a surgical outpatient department. They do not necessarily represent a cross-section of the population, but they do represent that social grade from which came the poisoning cases.

Case Histories

As this study involves a subjective analysis of case histories, it is advisable to show in summary the main facts from which conclusions are drawn. Where the mother made a graphic statement, it is quoted verbatim.

Case P1. A boy, 3 years, took 'dexedrine' tablets. 'Him? He's full of soap and buttons for all I know.' In answering a follow-up letter, the mother wrote, 'I am still extracting safety-pins, buttons, screws from toothpaste tubes, etc., from his mouth at all times of day.' He had previously taken aspirin tablets.

Case P2. A girl, $1\frac{1}{4}$ years, took barbiturate tablets. 'Terrible' for putting things in her mouth, 'bits off the floor or anything she can pick up.'

Case P3. A boy, 2 years, took aspirin tablets. He eats anything he sees in the way of clean food, but does not have pica, and does not show other unusual oral traits.

Case P4. A girl, $2\frac{1}{4}$ years, took laxative pills containing strychnine. She had no exaggerated oral tendencies.

Case P5. A girl, 5 years, took barbiturate tablets. She carried her feeding bottle about with her until the age of 3 years, and sucked it when not actively engaged in play. Had previously suffered from lupin poisoning, and had eaten rowan berries. A sister of Cases P6 and P7.

Case P6. A boy, 3½ years, took barbiturate tablets. A brother of Cases P5 and P7. 'I made sure I took *his* bottle away.' Takes two hours over each meal, 'Not because he doesn't like it, doctor. He always finishes it. He just chews and chews away at it.' Previous lupin poisoning,* and had eaten rowan berries.

Case P7. A boy, 1¼ years, took barbiturate tablets. A brother of Cases P5 and P6. His bottle also was 'taken away'. 'He eats bricks or earth or anything.' Had previously eaten rowan berries, but was not ambulant at the time of the lupin episode.

Case P8. A boy, 2½ years, took laxative tablets containing strychnine. No exaggerated oral traits.

Case P9. A boy, 1¾ years, took 'lysol'. 'He's put things in his mouth since he's walked. I've got to watch him all the time. It's usually things like crusts out of the gutter.' 'He's a greedy eater, you have to slow him down.' He was well-nourished, 3½ lb. over the expected weight for his age.

Case P10. A boy, 3 years, took 'thawpit'. Sucks his fingers whenever he finds anything soft or silky in his hand. From the description, this sounds like a conditioned reflex. For two weeks before the poisoning episode he had been taking a soft toy to bed with him. He used it as a breast substitute, holding it with both hands while sucking his thumb. Previously, he had a similar routine with a handkerchief.

Case P11. A girl, 2 years, took quinine tablets. She sucked a comforter from the age of 6 weeks. One week before the poisoning episode it was taken away from her, 'as she was getting worse instead of better'. Thereafter, she had 'never stopped eating', although previously a poor eater.

Case P12. A boy, 2½ years, took camphorated oil. He eats old bread off the floor, drains 'empty' bottles, and is much more prone to put things in his mouth than any of his three siblings.

Case P13. A girl, 2¼ years, took 'black laxative tablets'. She has a tendency to put things in her mouth, and her parents had tried particularly to keep medicines from her as a result. She eats coal. She has a ritual with fluff picked off the floor. First, she stuffs it up her nose, then she pulls it down again and eats it. She is fascinated by squeezing snails and slugs.

Case P14. A girl, 2¼ years, took chocolate laxative. She had no oral tendency until admitted to hospital shortly before the poisoning episode. While in hospital, an oral tendency appeared and became so marked that the ward sister specifically warned the mother about it. The symptom had persisted at home in the six weeks since discharge, and she had begun to eat sand.

Case P15. A girl, 2¾ years, took barbiturate tablets. Very similar to Case P14. Since discharge from a fever hospital six weeks previously, she had taken to sucking her fingers by day and night, at least four at once. Simultaneously, she pulled and twisted her ears, which appeared normal on examination.

Case P16. A girl, 1½ years, took ferrous sulphate tablets. Oral tendencies not marked. Still takes feeding bottle to bed. Arrived in hospital at 10 p.m., alert, confident and sucking a bottle.

Case P17. A boy, 4 years, took barbiturate tablets. He had just been referred to hospital because of recurrent asthma. A highly-strung child, he is always sucking a thumb or fingers, always picking things up and putting them in his mouth.

Case P18. A girl, 10 years, took a dry-cleaning agent. The liquid was the colour of lemonade and in a lemonade bottle. The child asked permission to drink it. No unusual oral traits.

Case P19. A boy, 1¾ years, took turpentine substitute. No exaggerated oral traits.

Case P20. A boy, 2¼ years, took travel sickness tablets (hyoscine). 'Is always biting at pencils and golf-balls.' He was nearly 2 years before relinquishing his bottle. His parents then gave him a hammer and told him to bash his bottle, which he did, apparently without regrets. For one month before the poisoning he had been demanding extra food between meals.

Case P21. A boy, 1¾ years, took turpentine substitute. 'I spend all my day watching him, I was glad to get rid of him when he was in hospital.' He is 'always after things' and will drink 'out of every bottle if he gets the chance.' Takes feeding bottle to bed with him. He also takes a doll and pretends to feed it with the bottle. Constantly nips, kicks and bites his mother.

Case P22. A boy, 1¾ years, took turpentine substitute. 'Out of hand,' but no exaggerated oral traits.

Case P23. A girl, 1½ years, took eardrops. Has to be checked frequently for putting things in her mouth, and in this respect is much worse than her two siblings.

Case P24. A boy, 5 years, took moth-balls. He has always been a thumb-sucker, and continues to suck it even in the daytime. He chews the corners of his shirt and pyjamas and is always asking for food. He is no longer allowed outside to play, as 'he eats old crusts out of pails' and has recently taken to eating bulbs which he has pulled up in the neighbours' gardens. Medicines have been kept rigidly in a locked cupboard. There is evidence in the early feeding history of a very strong oral tendency.

* As the writer has failed to find any written account of lupin poisoning, it seems pertinent to remark that the symptoms are very like those of laburnum poisoning.

TABLE 1

ORAL TRAITS IN CONTROL SERIES

Case No.	Sex	Age (years and months)	Oral Traits	Severity of Symptoms	Classification (see Table 2)
C 1	M	1 8	No abnormality	Absent	A
C 2	M	2 5			
C 3	F	2			
C 4	F	3 11			
C 5	M	2 1			
C 6	M	2 3			
C 7	M	2			
C 8	F	2 11			
C 9	F	3 6			
C10	M	3 8			
C11	F	3 8			
C12	M	2 4			
C13	M	2 9	Still sucks fingers, but only when tired	Mild	B
C14	F	2 2	'Fierce' at breast, sucks fingers at night, has 'breast substitute' sleep ritual	Moderate	
C15	F	1 8	Sucks fingers by day	Mild	
C16	M	3 1	Sucks fingers when tired, 'breast substitute' sleep ritual till aged 2 years	Mild	
C17	M	1 11	Sucking movements of mouth in bed, no object put in mouth	Mild	
C18	M	3	Has reverted to night bottle, or comforter in bed, since birth of second baby	Marked	
C19	M	1 7	Still has 'night bottle'	Mild	F
C20	M	2	Puts small objects such as buttons in mouth	Mild	
C21	M	2 5	Sucks fingers by day, very large appetite, bites hard objects, people and cushions	Marked	D
C22	F	2 8	For one month, biting nails and gnawing large hard objects	Mild	C
C23	M	1 7	Bites other children, their clothes and his cot	Moderate	C
C24	M	3 10	Pica till aged 2 years	Marked	G
C25	M	3 8	Fierce feeder at bottle, pica till aged 1½ years, gnaws hard objects, sucks fingers, has sleep ritual	Marked	G

Case P25. A girl, 1½ years, took moth-balls. Sister of Case P24. 'Puts things in her mouth when she sees her brother doing it.' When angry, she bites. 'She has a wicked little heart.'

Controls

The histories taken from the controls have been arranged in tabular form (Table 1). The numbering does not represent the order in which the histories were taken.

Conclusions

In comparing the results from controls and poisoning cases, both the type and the severity of the oral symptoms have been considered. In Table 2 the types are compared. The classification used is a utilitarian one, specifically designed to cover the cases in the present series, and making no claim to include all forms of oral abnormality.

The significance of oral traits in childhood is not yet fully understood, and it is thus impossible to differentiate in every case between normal, an exaggeration of normal and definitely abnormal oral symptoms. In the present series, cases in which it is doubtful whether the oral traits are exaggerated or not fall mainly into Category B. If these cases, except for C18, be regarded as normal, then 18 cases (72%) in the control series are orally normal, as opposed to six poisoning cases (24%). If they be regarded as exaggerations of normal, the figures become 48% and 20% respectively. At the other end of the scale, 10 poisoning cases (40%) show pica compared with two cases (8%) in the control series.

TABLE 2

TYPES OF ORAL SYMPTOM

Classification	Controls (No. of Cases)	Poisonings (No. of Cases)	Case Nos. in Poisoning Series
A. No oral abnormality	12	5	P4, P8, P18, P19, P22
B. Finger-sucking, sucking movements of mouth, sleep ritual at night only	7	1	P16
C. Aggressive use of mouth, i.e., biting people or hard objects	2	1	P25
D. Group C, with traces of Group F	1	1	P20
E. Group F, with traces of Group C	0	1	P17
F. Use of mouth in self-gratification, i.e., tasting, overeating, gentle sensation, sleep ritual seen in daytime ..	1	6	P3, P5, P6, P10, P11, P15
G. Pica	2	10	P1-2, P7, P9, P12-14, P21, P23-4
Total ..	25	25	

Considering the rest of the classification, it appears

that use of the mouth for self-gratification is found in a group of children where the incidence of pica is abnormally high. On the other hand, aggressive use of the mouth, for example, biting, is not particularly related to pica nor are the finger-sucking sleep rituals of early childhood.

A further comparison between the controls and the poisoning cases can be made on the basis of the severity of the oral symptoms. In some of the poisoning cases, e.g., P1 and P2, the oral history burst from the mother in a way which showed the symptoms to be severe, whereas the rather grudging admission of similar oral traits in some of the controls suggested that the symptoms were mild. In grading the control series the cases have been considered against a background of potential poisoning. Thus Case C18, not particularly striking when taken out of its context, has been graded as 'marked' as the child showed a reversion to a previous habit, as shown also in Cases P10, P14 and P15. The oral symptoms in the poisoning group, as well as being more serious in type than in the control group, were more striking in their severity, as can be seen from Table 3.

TABLE 3
SEVERITY OF ORAL SYMPTOMS

Severity	Controls (No. of Cases)	Poisonings (No. of Cases)	Case Nos. in Poisoning Series
No symptoms ..	12	5	P4, P8, P18-19, P22
Mild ..	7	4	P3, P16, P23, P25
Moderate ..	2	1	P1
Marked ..	4	15	P2, P5-7, P9-15, P17, P20-21, P24

Discussion

Attention has so far been focused on the part played by exaggerated oral tendencies in producing poisoning in the early years. There is, however, further suggestive evidence to be obtained from the small group of five children (or six, if Case P16 be included), who poisoned themselves without evidence of abnormal oral traits. Three of these children took poison in liquid form, which is relatively uncommon. The other three took either pil. aloin co. or ferrous sulphate tablets, and it has been shown (Craig and Fraser, 1953; Craig, 1955) that the three poisons most dangerous to children at present are ferrous sulphate, the antihistamines and strychnine in the form of compound pills. Thus the three children who took the most dangerous poisons in the present series happened to show little or no oral abnormality, and came to no harm. This contrasts with Cases P5, P6 and P7, a family with strong oral tendencies, who were all in coma as the result of taking barbiturates, a poison which is relatively innocuous in childhood. The numbers involved in this comparison are too small for any valid conclusion to be reached, but the evidence can be combined with the more definite evidence previously obtained, and a theory concerning the aetiology of poisoning in childhood can be postulated.

It appears that children who poison themselves can be divided into two groups:

(1) A small group of normal, exploratory toddlers who may take poison, usually in the form of attractive tablets or liquid from a bottle, but who taste or chew the substance and, in the majority of cases, reject it before coming to harm.

(2) A large group of toddlers who show exaggerated oral traits, amounting to pica in about 50%, and who poison themselves indiscriminately with tablets of any kind. Tablets attract them more than liquids, and, should they have access to attractive tablets such as ferrous sulphate, they would be particularly liable to bolt them in lethal quantities. The gourmet lives, the glutton dies.

This theory is, of course, complementary to accepted theories which stress the necessity of keeping poisonous substances away from children.

The exaggerated oral tendencies of the poisoned children were in many cases part of a widespread psychological disturbance. Three of the children came from a broken home; two others developed their symptoms while in hospital. In some cases the mothers' statements betray an unhappy parent-child relationship. However, a full psychological investigation was beyond the scope of the present study. Furthermore, an attempt to evaluate the feeding histories of the poisoned children was a failure, as the memory of the mother for the feeding details of two years before was too clouded for an accurate assessment to be made.

It should be clearly stressed that, even if one accepts the importance of the oral factor in poisoning, there is no good reason for relaxing general precautions against poisoning. Rather should they be intensified, particularly as the oral factor cannot be made the basis of propaganda for parents. On the other hand, it is highly desirable that anyone dealing with children should regard a poisoning episode not just as an accident that could happen to anyone, but as a significant milestone in the development of one particular child.

Summary

The case-histories of 25 poisoned children are reviewed, and it is found that there is a much higher

incidence of exaggerated oral traits, often amounting to pica, in this group than in a control series.

It is stressed that this is no reason for relaxing the customary precautions against accidental poisoning in childhood.

The theory is put forward that there are two main groups of poisoned children. There is a large group, showing exaggerated oral traits, and a smaller group showing no such abnormality. The individual risk of death is probably greater in the former than in the latter group.

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THE EFFECT OF PANCREATIN THERAPY ON FAT ABSORPTION AND NITROGEN RETENTION IN CHILDREN WITH FIBROCYSTIC DISEASE OF THE PANCREAS

BY

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For many years substitution therapy with various preparations of the pancreas has been given to children with fibrocystic disease of the pancreas as a routine treatment. This is recommended in most textbooks of paediatrics (Rapoport, 1954; Norman, 1954), although the practice has been based on the clinical evaluation of the results rather than on any objective study of the results of metabolic balances. May (1954) claimed that better results were obtained by the administration of a generous high-protein diet without pancreatin, which he believes impairs the appetite.

The study was undertaken in order to find out, by means of metabolic balances, what effect pancreatin replacement therapy does in fact have on fat and nitrogen absorption and retention.

Selection of Cases

The children studied had all been under observation for some years and clinically appeared typical cases of fibrocystic disease. In every case but one (Case 11, L.B.) examination of the duodenal juice had been satisfactorily carried out and had shown complete absence of trypsin, and in those cases in which the enzyme estimation had been done, absence of lipase and amylase. It was essential for the purpose of the balance that the children should be continent of urine and faeces and be able to cooperate, so only children between the ages of 4 and 10 were chosen, but no special selection was made as regards sex or severity of the disease.

A few minor disturbances of health occurred among the children during the long study period and four suffered from respiratory infections requiring chemotherapy. Only one child proved such an unsatisfactory subject that the study had to be abandoned in her case.

Method

On each child three sets of balances were carried out, giving first no pancreatin, then 5 and 15 g. The order in which the balances were done was varied from case to case in order to use all six possible variations. The pancreatin was given four times daily immediately before meals, and was usually swallowed dry or stirred into a little cold milk or water. The pancreatin used was the usual hospital preparation of powdered pancreatin (B.P. triple strength) treated to form enteric-coated granules (Bodian, 1952; Norman, 1954). The nitrogen content of the pancreatin so prepared was repeatedly checked and found to contain 35 mg. nitrogen per gram of granules; the enzyme activity was also checked several times and found to be fully potent. The diet was kept constant throughout each balance and was the type of diet in amount and variation to which the child was accustomed. The fat and nitrogen content of the diet was calculated by the hospital dietitian from the tables devised by McCance and Widdowson (1940). All food was weighed The fat and nitrogen content of the diet was then checked by chemical estimation of these constituents in a whole day's food.

The fat and nitrogen balances were carried out concurrently, the fat for a minimum of eight days and the nitrogen for two consecutive five-day periods. Daily faecal fat estimations were carried out and the result expressed as the percentage absorption for each 24-hour period. To correct for any lag in intestinal absorption the three-day sliding mean of these percentages was calculated and, from these figures, the average percentage absorption for the whole eight days. The nitrogen output was estimated as a total for each five-day period, the urine being pooled and volumetric samples taken of the homogenized faeces which were then also pooled. Carmine was used to mark the beginning and end of each balance period. An average was calculated for the two five-day periods.

The children were cared for in one special metabolic ward and led a normally active life, attending hospital school and having outings. Several days were allowed after admission for the child to settle down in the ward

TABLE 1
FAT BALANCES AND AVERAGE PERCENTAGE FAT ABSORPTION

Case Number		1	2	3	4	5	6	7	8	9	10	12	
Age in years		8	$5\frac{7}{12}$	$8\frac{1}{2}$	$6\frac{11}{12}$	$7\frac{7}{12}$	$8\frac{11}{12}$	$7\frac{1}{2}$	$4\frac{7}{12}$	$5\frac{1}{2}$	$6\frac{1}{2}$	10	
Sex		M	F	F	M	M	F	F	F	M	M	M	
Average fat intake (g.)		79·6	62·2	61·1	70·2	69·5	72·4	65·1	63·9	56·4	67·9	89·7	
	Pancreatin (g. q.d.s.)												Average for All Cases
Average % Fat Absorption	0	40	57	37	54	65	37	42*	69	43	31	32	46
	5	52*	61	56	71	78	65	69*	88	65	57	58*	67
	15	62	69*	66	78	74*	67*	75	86*	76	55	69	71

* Indicates some disturbance of health during balance.

and become stabilized on the measured diet and there were also rest periods between balances during which time they were stabilized on the different amounts of pancreatin. In addition, three chylomicron curves were carried out on each child, without pancreatin and with 5 and 15 g. given with the fatty meal.

Clinical observations were made on the children during the balances and any disturbances in health noted. They were weighed every third day.

Discussion of Results

Twelve children were studied. The results of the fat and nitrogen balances on one of these (Case 11, L.B.) will be discussed separately. The other 11 are discussed as a group.

Fat Absorption. The results of the fat balances showed that the fat absorption was considerably increased by the addition to the diet of 5 g. pancreatin four times a day before each meal, whilst 15 g. in most cases caused a further but smaller increase. These results were so clear that the figures were not analysed further.

Disturbances in health were quickly reflected in the fat balances. For example, Case 12 developed an upper respiratory infection on the eighth day of the 5-g. balance. A tachycardia had been noted on the seventh day, but the fat absorption on the sixth day had already dropped to 39% and the three-day sliding mean showed the following result: 55%, 79%, 86%, 62%, 31%, 37%. The decrease in fat absorption occurred in the absence of any antibiotics.

Nitrogen Absorption. The figures for the average faecal excretion of nitrogen (Table 2) show that this dropped to just under a half with the addition of 5 g. pancreatin to the diet. No further significant diminution in the faecal nitrogen excretion occurred when 15 g. were given.

TABLE 2
NITROGEN BALANCES

Pancreatin (g. q.d.s.)	Mean Output of Nitrogen in Faeces (g.)	Standard Error of Mean
0	23·10	1·24
5	10·78	1·02
15	10·27	1·26

Mean difference without pancreatin and with 5 g. q.d.s. −12·32 g. Standard error 1·07 ($P<0·001$).

Mean difference with pancreatin 5 g. q.d.s. and 15 g. q.d.s. −0·51g. Standard error 1·86 ($P>0·7$).

The nitrogen retention (Table 3) was considerably increased by the administration of 5 g. pancreatin, and even more when the larger dose of 15 g. was given. The average nitrogen retention was in fact more than six times as great with the larger dose of pancreatin as with the smaller dose. This increased retention could have been due either to increased intake of nitrogen or to diminished loss in the stools. As the faecal loss of nitrogen dropped to just under half whether 5 or 15 g. were given, the increase in nitrogen retention could not entirely have been due to pancreatic enzyme activity. On the other hand, the addition of the maximum dosage of pancreatin of 60 g. daily contributed to an approximately 25% increase in the average daily intake of protein, which was 55·3 g.

TABLE 3
NITROGEN BALANCES

Pancreatin (g. q.d.s.)	Mean Balance of Nitrogen (g.)	Standard Error of Mean
0	− 3·75	1·3
5	+ 1·61	1·44
15	+10·77	1·47

Mean difference without pancreatin and with 5 g. q.d.s. −5·36 g. Standard error 2·11 ($P>0·02$).

Mean difference with pancreatin 5 g. q.d.s. and 15 g. q.d.s. −9·16 g. Standard error 1·62 ($P<0·001$).

The effect of ill health on nitrogen retention was clearly seen even in those cases where the disturbance was slight. For example, Case 7 had a mild attack of abdominal pain with a temperature of 99·4° F. on the ninth day of the balance study without pancreatin. When the child recovered, the balance with 15 g. four times daily was begun and this showed a low nitrogen retention for the first five days. The balance was then continued for two further five-day periods and showed increasing nitrogen retention.

Chylomicron Curves. These showed slight but definite improvement when pancreatin was given (Fig. 1) though even so the curves obtained did not approach normal.

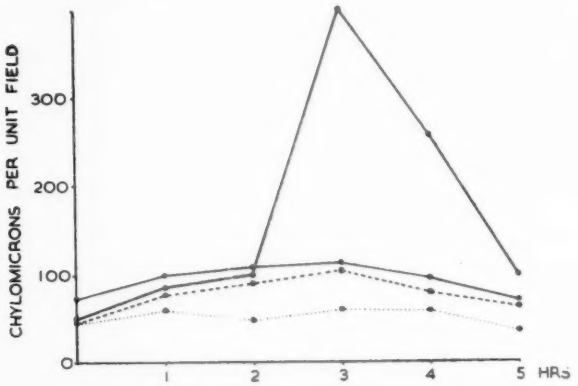

FIG. 1.—Curves showing average chylomicron counts.

..... Without pancreatin.
---------- With 5 g. of pancreatin.
——— With 15 g. of pancreatin.
Normal curve.

Weight. The children showed marked gain in weight when the largest amount of pancreatin was given, corresponding to the increased nitrogen retention and improved fat absorption (Fig. 2). The weight tended to remain more or less stationary when 5 g. of pancreatin were given and to fall when pancreatin was withheld. It is evident that although supposed to be receiving an ample high-protein diet, most of these children probably had too low a protein intake.

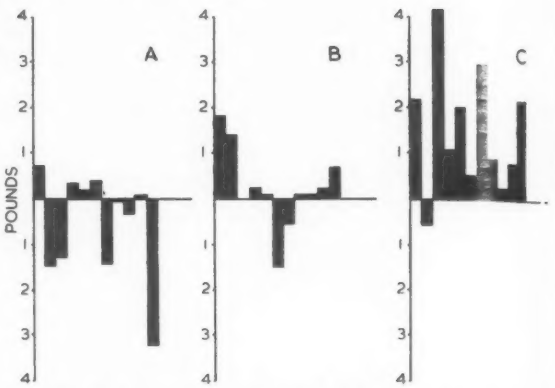

FIG. 2.—Weight gain or loss of each child during investigation.
A. Without pancreatin.
B. With 5 g. of pancreatin four times daily.
C. With 15 g. of pancreatin four times daily.

Faeces. As was to be expected, these children passed enormous stools with undigested food and fat in them, but it was found that the volume of the stools dropped to about a third on 15 g. pancreatin four times daily and, though still unpleasant in smell, were more formed in character.

General Health. Except where indicated, the children all remained in good general health. Cases 1, 2, 7, 8 and 12 had mild upper respiratory infections, Case 5 vomited during the 15 g. balance, Case 6 had loose stools and Case 7 abdominal pain and slight fever. It was observed that a few of the children complained of abdominal discomfort when the large dose of pancreatin was given.

CASE 11. This girl, aged 7 years 9 months, was of special interest clinically because she appeared to be a case of fibrocystic disease of the pancreas with fairly severe involvement of the respiratory tract. An older sister has proven fibrocystic disease with severe pulmonary involvement. The child studied, however, was found to have a normal content of amylase in the duodenal juice, and tryptic digestion of 2 ml. of 7·5% gelatin to a dilution of 1 in 400, which is within normal limits, although only 17 units of lipase were present per 100 ml. juice (normal 38-100 units). The results of the metabolic balances are given in Table 4. These results show that her fat absorption was unaffected by pancreatic

TABLE 4

RESULTS OF METABOLIC BALANCES IN CASE 11

Pancreatin	Intake Nitrogen (g.)	Output Nitrogen (g.)			Intake Nitrogen (g.)	Output Nitrogen (g.)			% Fat Absorption	Weight Gain or Loss (oz.)
		Urine	Faeces	Balance		Urine	Faeces	Balance		
0	43·7	36·1	7·3	+ 0·3	43·7	29·3	9·9	+4·5	88	− 4
5	47·2	38·5	10·2	− 1·5	47·2	33·9	7·4	+5·9	84	+ 14
15	54·2	32·0	10·5	+11·7	54·2	39·1	8·1	+7·0	84	+ 10

therapy, but her nitrogen retention was improved and she gained 24 oz. in weight when given pancreatin.

In this case there was very little difference in the faecal nitrogen in the three sets of balances and the improved nitrogen retention must have been due to the utilization of the protein of the pancreatin as a food.

Conclusion

It was concluded from these studies that the absorption and utilization of fat and protein in children with fibrocystic disease of the pancreas was improved by pancreatic therapy as shown by gain in weight, positive nitrogen balances and increased fat absorption. Five grams of pancreatin with each meal is probably the largest dose required, any increase in this amount resulting in very little improvement in enzymatic activity. Apparent clinical improvement on a larger dose, as shown by increase in body weight, is due to the increased nitrogen intake obtained from the pancreatin. Intercurrent illnesses diminish absorption of fat and nitrogen even if large doses of pancreatin are being given.

We would like to acknowledge the spirit shown by the children and their parents in agreeing to a prolonged stay in hospital for the sake of this work. We also wish to thank Miss Dilliston and her staff from the diet kitchen for their help, and Dr. Cedric Carter for his assistance in the statistical analysis of the results. The work was made possible by grants from Messrs. Cow and Gate and the Research Committee of The Hospital for Sick Children, to whom our thanks are due.

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NON-PANCREATIC LIPASE IN CHILDREN WITH PANCREATIC FIBROSIS

BY

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It has been shown that children with pancreatic fibrosis who have no pancreatic lipase at all may absorb a considerable proportion of dietary fat (Shohl, 1948; Andersen, 1945a and b; Ross, 1955). In addition it has been demonstrated by Andersen (1945a) that there may be a considerable amount of hydrolyzed fat in the stools of children with pancreatic fibrosis. These findings would indicate the presence of non-pancreatic lipase in the gastro-intestinal tract derived either from dietary or non-dietary sources.

Possible sources of dietary lipase have not been adequately investigated. Although Green (1890) demonstrated lipase in the germinating seeds of the castor bean, we could find no reports on the lipase content of various fresh fruit and vegetables which are commonly used in human diets. Freudenberg (1929) showed that there was lipase in human and cow's milk and claimed that the enzyme in milk was activated by a lipokinase in human gastric juice. Several possible sources of non-dietary lipase in the gastro-intestinal tract have been studied. Schønheyder and Volqvartz (1944) demonstrated lipase in both gastric juice and gastric mucosa from infants and adults: they showed that only the lower triglycerides were hydrolyzed to an appreciable degree by this lipase and that the optimum *p*H was 5·5 to 5·8. It has been questioned, however, if gastric lipase is secreted by the stomach or if it enters the stomach by regurgitation from the duodenum (Wolman, 1943). That intestinal bacteria might be a source of lipase in children with pancreatic fibrosis was suggested by Andersen (1945a) who found that a considerable degree of hydrolysis of faecal fat occurred in stools which were left standing for 48 hours at room temperature.

The object of the present study was to investigate the activity of several possible sources of dietary and non-dietary lipase in the gastro-intestinal tracts of children with pancreatic fibrosis.

Materials and Methods

Estimation of Lipase. To 5 ml. of phosphate buffer containing 0·5% bile salts at *p*H 7·8 in a 50-ml. stoppered conical flask was added 1 ml. of acid-free olive oil. The lipase preparation was then added and the mixture shaken for 30 minutes at 37° C. It was then acidified and extracted with 20 ml. of benzene. A 10-ml. sample of upper benzene layer was titrated with 0·05 N tetramethylammonium hydroxide in alcohol. A control was made in the same way but with the addition, before digestion, of a few drops of concentrated hydrochloric acid to inhibit lipase activity. The titration figure in ml. gave the units of lipase in the sample (Frazer, Sammons and Thompson, 1955). As it was found that the error of this method was ±0·05 units, any reading below 0·1 was considered as nil.

Dietary Lipase. Lipase was estimated in the following items of diet.

MILK. Both human and cow's milk were investigated: representative specimens of human milk were obtained from the whole milking of each of 12 mothers at varying stages of lactation; similar specimens were obtained from six cows. Each specimen was thoroughly mixed and its lipase content estimated before and after pasteurization.

FRUITS. These comprised apple, banana, pear, orange and tomato: 1 g. of each, finely chopped, was used for the estimation.

Non-dietary Lipase. Specimens of faeces and gastric juice were obtained from seven children with pancreatic fibrosis who had not received pancreatin during the preceding four days. Each child had no pancreatic enzymes whatever in duodenal juice: lipase was estimated by the method described above, trypsin by the method of Tomarelli, Charney and Harding (1949). The fat absorption figures in these children ranged from 32 to 60% of their dietary fat intake: fat absorption was assessed by fat balance studies for periods of five to 10 days, faecal fat being measured daily by an adaptation of the fatty acid method of Kamer, Bokkel Huinink and Weyers (1949) as described by Anderson, Frazer, French, Gerrard, Sammons and Smellie (1952).

FAECES. As we found that lipase was rapidly destroyed

in faeces at room temperature, a complete fresh stool collection was obtained from each child. This was immediately homogenized with water to a known volume and lipase estimations were carried out on 1-ml. samples of each homogenate.

GASTRIC JUICE. A specimen was obtained from the fasting child and was kept at 0° C. Lipase was estimated in 0·1 ml. of gastric juice within two hours of collection. As we found that gastric lipase activity, using olive oil as substrate, was optimal about *p*H 3, the buffer employed was acid sodium citrate at *p*H 3·0.

CULTURES OF INTESTINAL BACTERIA. Cultures of various intestinal bacteria (*Esch. coli*, β-haemolytic *Streptococcus*, *Streptococcus faecalis*, *Streptococcus viridans* and *Staphylococcus aureus*) were obtained from the faeces of a child with pancreatic fibrosis. A specimen of the faeces was plated on blood agar, on blood agar after treatment of the faeces with toluene to suppress the Gram-negative organisms and on MacConkey's agar. After incubation for 24 hours at 37° C., representative individual colonies were picked off and subcultured in (*a*) glucose broth and (*b*) glucose broth containing 0·5% nut oil. After incubation for 18 hours at 37° C., 1 ml. of each subculture was used for estimation of lipase. This method would, of course, only detect exo-lipase and not endo-lipase in bacterial cells: it was considered, however, that bacterial endo-lipase would not be concerned in digestion.

Chylomicrographs. Counts of the fat particles in the blood after a standard fat meal were carried out by the chylomicrograph technique described by Frazer and Stewart (1939): details of the procedure have been given in a previous report (Ross, 1955).

Results

Dietary Lipase. This was demonstrated as follows:

MILK. The lipase content of the samples of human milk is shown in Table 1 and of the samples of cow's milk in Table 2. In the unpasteurized samples of human milk the lipase ranged from 0·35 to 0·95 units per 1 ml. (mean 0·56 units) compared with a range of 0 to 0·3 in the unpasteurized samples of cow's milk. After pasteurization there was a considerable reduction in the lipase content of both human and cow's milk samples. Moreover, it was found that there was a rapid loss of milk lipase at room temperature: in a sample of human milk at 17° C. the lipase fell from 0·53 units at the time of collection from the breast to 0·26 units at four hours and 0·18 units at nine hours.

TABLE 1
LIPASE IN HUMAN MILK

Mother	Week of Lactation	Lipase (units per 1 ml.)	
		Unpasteurized	Pasteurized
1	1	0·4	0
2	1	0·5	0
3	1	0·75	0·1
4	3	0·95	0·1
5	4	0·8	0
6	5	0·4	0
7	6	0·4	0·2
8	8	0·8	0·1
9	10	0·35	0
10	11	0·5	0
11	15	0·4	0
12	16	0·5	0
	Means ..	0·56	0·04

TABLE 2
LIPASE IN COW'S MILK

Cow	Lipase (units per 1 ml.)	
	Unpasteurized	Pasteurized
1	0·1	0
2	0·1	0·1
3	0	0
4	0	0
5	0	0
6	0·3	0

Evidence that the lipase in fresh unpasteurized human milk may increase fat absorption in pancreatic fibrosis was obtained as follows. Chylomicrographs were carried out on an infant with this disease after feeds, quantitatively similar in fat content, of (*a*) unpasteurized human milk, (*b*) pasteurized human milk and (*c*) pasteurized cow's milk. From Fig. 1 it will be seen that the chylomicrograph after unpasteurized human milk showed a higher rise than those obtained after pasteurized human milk or pasteurized cow's milk. Unfortunately we were unable to confirm this finding by fat balance studies in a baby receiving fresh unpasteurized human milk as there was no breast-fed baby in the present series, nor could we obtain a completely fresh supply of

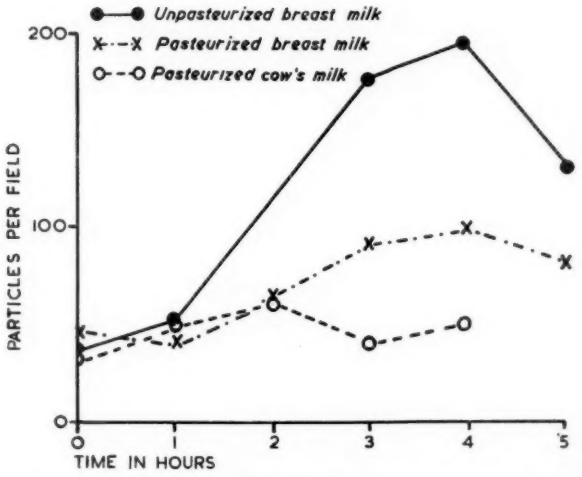

FIG. 1.—Chylomicrographs after milk feeds quantitatively similar in fat content, in a boy 8 months of age with pancreatic fibrosis.

human milk for the 10 days necessary for a fat balance study.

FRUITS. No lipase was detected in any of the fruits examined.

Non-dietary Lipase. The following gave useful results:

FAECES. From Table 3 it will be seen that lipase

TABLE 3
LIPASE IN FAECES OF CHILDREN WITH PANCREATIC FIBROSIS

Patient	Age (yrs.)	Mean Percentage Fat Absorption	Faecal Lipase (units)	
			Per 1 ml. Homogenate	Per 100 ml. Fresh Faeces
1	1½	52	0·53	106
2	1½	48	0·21	53
3	3½	52	0·1	27
4	4	39	0·44	88
5	4	58	0·64	134
6	5	32	0·58	174
7	6	60	0·10	24

was present in the faeces of all seven children. The possible sources of this enzyme seemed to be gastric juice, intestinal bacteria and succus entericus.

GASTRIC JUICE. No lipase was found in five out of the seven samples of fasting juice; the remaining two samples contained only traces of lipase—0·23 and 0·12 units respectively. From this it would appear that gastric juice provides no significant contribution to gastro-intestinal lipase.

INTESTINAL BACTERIA. No lipase was detected in any of the cultures under the conditions of the experiment either in glucose broth or glucose-oil broth.

Discussion

We have shown that, of various fresh foods commonly used in human diets, only unpasteurized milk contained lipase and that this enzyme was appreciably greater in human than in cow's milk. It was found that milk lipase was destroyed by pasteurization and that its activity decreased rapidly at room temperature. That the lipase in fresh human milk may play a part in lipolysis was suggested by the chylomicrograph findings after various milk feeds in an infant with pancreatic fibrosis: the chylomicronaemia was significantly greater after a feed of unpasteurized human milk than after feeds of either pasteurized human milk or pasteurized cow's milk. This would suggest that breast-fed infants with pancreatic fibrosis might have a greater fat absorption and hence more favourable nutrition than babies with pancreatic fibrosis who are artificially fed. Andersen (1938) and Lowe, May and Reed (1949), however, could find no difference between the nutritional state, as judged by weight gain, of breast-fed and artificially-fed babies with pancreatic fibrosis. In the present series of children with pancreatic fibrosis all were receiving pasteurized cow's milk preparations so that dietary lipase would play a negligible role in intestinal lipolysis.

We have shown that lipase is present in fresh faeces from children with pancreatic fibrosis. Its absence or presence in minute amounts in gastric juice from these children indicates that gastric juice is not an appreciable source of the enzyme. In addition, we have demonstrated that no exo-lipase was produced in cultures of several intestinal organisms from a child with pancreatic fibrosis. The lipase activity of 1,000 strains of 18 potentially pathogenic genera was investigated by Davies (1954) who found that only certain strains of staphylococci produced exo-lipase: she assessed lipase activity by demonstrating either a zone of clearing on a culture plate of nutrient fat agar or a blue zone on a plate of nutrient fat Nile blue sulphate agar. Our inability to demonstrate production of exo-lipase by the *Staphylococcus aureus* in the present study might be due to the fact that this strain belonged to the group from which Davies could detect no lipase production; on the other hand, her method of estimation might be more sensitive than ours. It is evident, however, that intestinal organisms are not an appreciable source of faecal lipase. Moreover, as fat absorption occurs in the small intestine and intestinal organisms are mainly limited to the large intestine (Cregan and Hayward, 1953), it is obvious that bacterial lipase would play little part in lipolysis of dietary fat. It seems that the enzyme is probably derived from the succus entericus: this deduction finds support in recent work by Singer, Sporn and Necheles (1954), who have shown, in dogs, that lipase is secreted by the jejunum.

Sammons, Ross and Wood (1955) have demonstrated the presence of a proteolytic enzyme in the stools of children with pancreatic fibrosis. They showed that this enzyme was probably derived from the succus entericus and was probably responsible for the considerable degree of protein digestion which has been demonstrated in children with pancreatic fibrosis (Frazer, McWeeney, Pover, Ross and Sammons, 1954). The present study suggests that the succus entericus is also responsible for the considerable degree of fat absorption which is found in this disease.

Summary

The fact that children with pancreatic fibrosis who have no pancreatic lipase at all can absorb a considerable proportion of dietary fat led us to

investigate various sources of dietary and non-dietary lipase in the gastro-intestinal tract.

Of the foods examined fresh unpasteurized milk was the only one which contained lipase: the enzyme was appreciably greater in human than in cow's milk. Pasteurization destroyed milk lipase and rapid loss of activity occurred at room temperature.

Lipase was present in the stools of these children but was absent in gastric juice and in cultures of intestinal organisms. It therefore appears that the enzyme is produced by the succus entericus.

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AN ANTHROPOMETRIC STUDY OF EDINBURGH SCHOOLCHILDREN

PART II: COMMENTS ON RESULTS

BY

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In Part I of this paper (Provis and Ellis, 1955), a description was given of the measurements of more than 1,700 Edinburgh schoolchildren in 1952-53, these children being a stratified sample of the whole school population. Tables 1 and 2 in that paper summarized the various measurements and indices according to age group and sex, and Figs. 1 to 4 illustrated the age-group means for three linear measurements and two measures of width.

Though group means do not describe the individual child's increments or growth pattern with age, the group means together with the variability of measurements of the individual children in each group give an indication of the range of 'normal' measurements at different ages. It seems worth while, therefore, to make some comments on the points of special interest in the measurements of Edinburgh children, especially as cross-sectional surveys of British schoolchildren have in the main been limited to measurement of height and weight, and very few data on body widths or on head measurements are available. The results which were tabulated in Tables 1 and 2 in Part I are discussed in more detail in the paragraphs which follow, and some additional diagrams are given, these being numbered Figs. 5 to 9 to form a sequence with the diagrams shown in Part I.

Length Measurements

Total Crown-Heel Length. The mean lengths and standard deviations for each year-group of boys and girls from 5 to 17 years were shown in Tables 1 and 2 (Part I). From ages 5 to 10 years there was little difference in the group means for boys as compared with girls, and for both sexes the increase with age was approximately linear. From the age of 10+ years, the girls' means began to overtake and exceed those of the boys. Though the differences were small they were consistent and continued until the age of 13+. From 14+ years onwards the boys' means continued to increase linearly whilst the increase in girls' means flattened out, so that each year the greater mean length for groups of boys became more marked.

In the earlier years, when boys' and girls' means were almost the same, the regression estimates were as follows:

Age (yr.)	7	8	9	10
Group mean length (cm.)	118·8	123·3	127·8	132·3

The variability of individual children's lengths around the group mean, as indicated by the standard deviation of each mean, can be quickly judged by the coefficient of variation (ratio of standard deviation to group mean). It will be seen in Tables 1 and 2 (Part I) that the coefficients of variation of length were relatively low and ranged mainly around 4% to 5%. That is to say, if two standard deviations on either side of the mean are taken as the main range which includes approximately 95% of the observations, the great majority of the children in each age-group had lengths within 10% of the group mean length.

Stem Length. The group means for stem length were consistently higher for boys than for girls until the age of approximately 11 years. From ages 11 to 15 the group means for girls increased rapidly, and at 12 and 13 years the girls' means considerably exceeded those of the boys. From age 15 onwards, however, the boys' group means again overtook those of the girls and increased rapidly, so that at ages 16 and 17 the mean stem lengths for groups of boys were far greater than those for groups of girls. The pattern of increase of group mean stem length with age was to some extent similar for the two sexes in that, for both there was

at first an approximately linear increase, then an acceleration and more rapid rate of increase and finally a deceleration and flattening out. In girls' means the accelerated rate of increase began at about 10+ years, nearly three years earlier than in boys' means which did not exhibit the accelerated rate of increase until about 13+ years. Similarly, the flattening out and slower rate of increase began earlier in girls' group means than in boys'.

In the first few years, when increase in group means was fairly steady, the regressions gave the following estimates:

Age (yr.)	6	7	8
Group mean stem length (cm.):			
Boys	64	66	68
Girls	63·5	65·5	67·5

The variability of individual children's stem length in relation to the group mean, as indicated by the coefficient of variation, was very similar to the variability of crown-heel length, though perhaps very slightly lower. At ages up to 13 years the coefficient of variation approached 5%; for boys from 14 to 16½ years the variability increased a little.

Span. The group mean span for boys up to the age of 12 years or so was consistently a little higher than for girls. At ages 12 and 13 the girls' means approached and even overtook those of the boys, but from 14 years and onwards the group means for boys rose considerably higher than for girls and the differences increased progressively. The pattern of increase of group mean span for boys was almost linear throughout the age range from 5 to 16 years. For girls' means the pattern was one of almost linear increase up to the age of 13, and then a flattening out for 14-year-olds and onwards.

In the middle period of 10 to 12 years, when the group means for boys were only a little greater than for girls, the regressions gave the following estimates for boys' mean span:

Age (yr.)	10	11	12
Group mean span (cm.)	133·5	139·0	144·5

The variability of the span of individual children relative to the mean for each age-sex group, as shown by the coefficient of variation, was very similar to the variability of total length and very slightly greater than that of stem length. As with the latter, so with span the variability of individual boys' measurements at ages 14 to 16 years was a little greater than for girls or for younger boys.

Relationships between Lengths

Ratio of Stem Length to Total Length. The proportion which stem length forms of total length is known to vary with age and relative growth rate. Fig. 5 illustrates the changes in ratio of stem length to crown-heel length for groups of boys and girls of different age. Though the group mean ratios for both sexes varied only between 0·58 and 0·52, within that range an age pattern was clearly discernible. Both for boys and for girls, the mean ratio fell during the earlier years, stabilized during the period of puberty, and rose very slightly in the oldest age groups. The difference between the sexes, however, is apparent. For age groups under 11 years the group means for girls were consistently a little lower than those for boys, whilst for age groups over 11 years the girls' ratios were markedly higher than the boys'. The patterns seem to confirm the earlier onset of puberty in girls and their greater relative stem length than leg length during this period.

From the data obtained in this study, the boys' means formed a more regular pattern than those of the girls. This was found also in most of the other measurements taken in this investigation. Whether this is due to greater variability in girls' measurements or whether it is partly due to less successful measuring of female subjects is a matter for speculation.

Ratio of Span to Total Length. Fig. 6 shows the changes in the mean ratio of span to length with changing age. As might be expected, the ratio for both sexes lay very close to unity, the range being from 0·97 to 1·02. Again the pattern for boys was more clearly apparent than that for girls, but for both sexes the mean ratio rose sharply for the youngest age groups, and more slowly from 9 years or so. The mean ratio for girls was consistently less than that for boys; for the latter the group mean reached 1 at about 8½ years, whilst for girls the ratio did not reach 1 until nearly 12 years.

Width Measurements

Biacromial Diameter. From a scrutiny of Tables 1 and 2 (Part I) it is apparent that the group means of biacromial diameter for boys and girls of similar age were very similar until the age of approximately 11 years. For age groups from 5 to 11 years the group means rose fairly steadily, and for boys a similar rate of increase continued until about 14½ years. For girls, however, there was a more rapid increase in the means from 11½ to 13½ years, and then a marked flattening out in the rate of increase

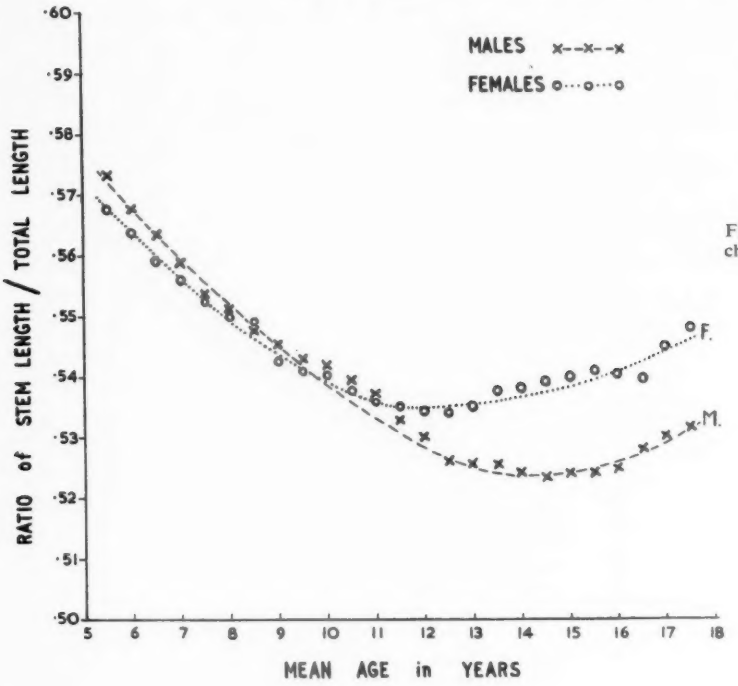

FIG. 5.—Stratified sample of Edinburgh schoolchildren. Relationship between stem length and total length by age and sex.

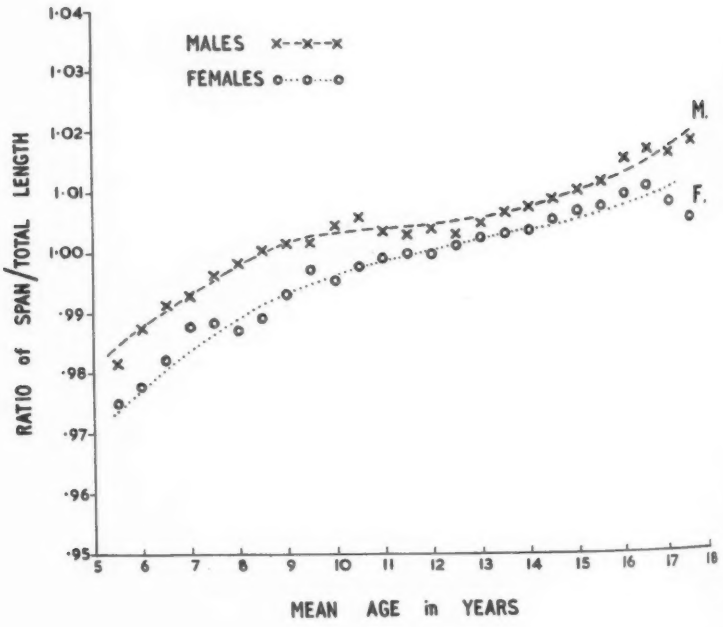

FIG. 6.—Stratified sample of Edinburgh schoolchildren. Relationship between span and total length by age and sex.

from 14 years onwards. Thus, for age groups from $11\frac{1}{2}$ to nearly 14 years the mean biacromial diameters for girls consistently exceeded those for boys. From $14\frac{1}{2}$ years onwards the boys' means rose at a much steeper rate than in the earlier years, so that the excess of boys' means over girls' increased rapidly.

During the middle years, when the means for the two sexes were very similar, the estimated values were as follows:

Age (yr.)	9	10	11
Group mean biacromial diameter (cm.)	28	29	30

The variability of biacromial diameter within

each age-sex group (as indicated by the coefficient of variation) was between 3½% and 6% for ages up to 9 years and a little greater at ages above 9 years. For the age groups 14 to 16½ years the variability of biacromial diameters among boys was rather greater.

Pelvic Width. As seen in Tables 1 and 2 (Part I) and Figs. 3 and 4, the mean intraspinous pelvic width for groups of boys and girls rose throughout almost the entire age range. From 5 years until 11+ years, the boys' means were a little greater than the girls', and the increase for both sexes was almost linear. From 11+ to 15 years the rate of increase of girls' means accelerated, and during these years the mean pelvic width of girls exceeded that of boys. From 15 years or so onwards, the rate of increase of boys' means accelerated slightly while for girls it slowed down.

At ages 9 to 11 years, when the mean pelvic width for boys and girls was very similar, the regressions indicated the following estimates:

Age (yr.)	9	10	11
Group mean pelvic width (cm.):			
Boys	21·0	21·7	22·4
Girls	20·8	21·5	22·2

The variability of individual children's pelvic width around the group mean was a little higher than the variability of length, and the standard deviations ranged mainly from 5% to 7% of the corresponding means. The greatest variability for both boys and girls appeared to be in the ages 12 to 15 years.

Weight

Tables 1 and 2 (Part I) and Fig. 7 below show that the mean weights for each age-group increased curvilinearly until 15+ years and thereafter increased less rapidly. From ages 5 to 10 the means for boys and girls were very similar, those for boys being perhaps very slightly greater. From 11 to 14 years the rate of increase of girls' means became steeper, and the excess of the girls' means over the boys' was most marked at ages 12+ to 13+ years. From 13+ years onwards the increase of the girls' means was less rapid while the boys' means increased more steeply, so that from 15 years onwards the group means for boys were considerably greater than the means for corresponding groups of girls.

In the middle period, 8 to 11 years, when the means for the two sexes were closest to each other, the regression for boys gave the following estimates:

Age (yr.)	8	9	10	11
Group mean weight for boys (kg.)	23·7	25·9	28·6	31·8

The variability of weights of individual children around the group means was considerable even in the youngest age groups and increased with age until 13 to 14 years. Even at ages 5 to 9 years the coefficients of variation ranged from 10% to 16%; that is to say, the majority of the children had weights within the range of 20% to 32% on either side of the group mean weight. At ages 12+ to 15+ years the coefficients of variation ranged from 15% to 19%, indicating even wider divergence of individual weights from group means.

Head Measurements

Length, Breadth, Circumference. For all three measurements the group means rose fairly steadily with age, the rise being almost linear for head breadth; and for all three measurements the boys' means were consistently greater than the means for groups of girls of similar age. Fig. 8 illustrates one of the head measurements, namely the increase of mean head length with age. The regressions gave the following estimated measurements:

Age (yr.)	8	9	10
Group mean head length (cm.):			
Boys	18·11	18·20	18·29
Girls	17·74	17·83	17·92
Group mean head breadth (cm.):			
Boys	14·22	14·30	14·38
Girls	13·93	14·01	14·09
Group mean head circumference (cm.):			
Boys	52·25	52·55	52·85
Girls	51·62	51·92	52·22

The variability of individual children's head measurements in relation to the group means was somewhat lower than the variability of body lengths and considerably lower than the variability of weight. For head length and breadth the coefficient of variation was between 2% and 4½%, and for head circumference the coefficient was between 2% and 3½%. In contrast with body lengths and weight, for the various head measurements there appeared to be no association of variability with age.

Ratio of Breadth to Length (Cephalic Index). Though for each of the separate head measurements the age group means formed very consistent patterns, the ratio of breadth to length of head of each individual child gave no pattern at all, nor was any regularity discernible in the age-group means of this ratio. For both sexes, the group means of head-breadth/length ratio ranged in the main between 0·782 and 0·793—a very narrow range within which it was difficult to perceive any consistent trends. Fig. 9 illustrates the means of the ratios for each

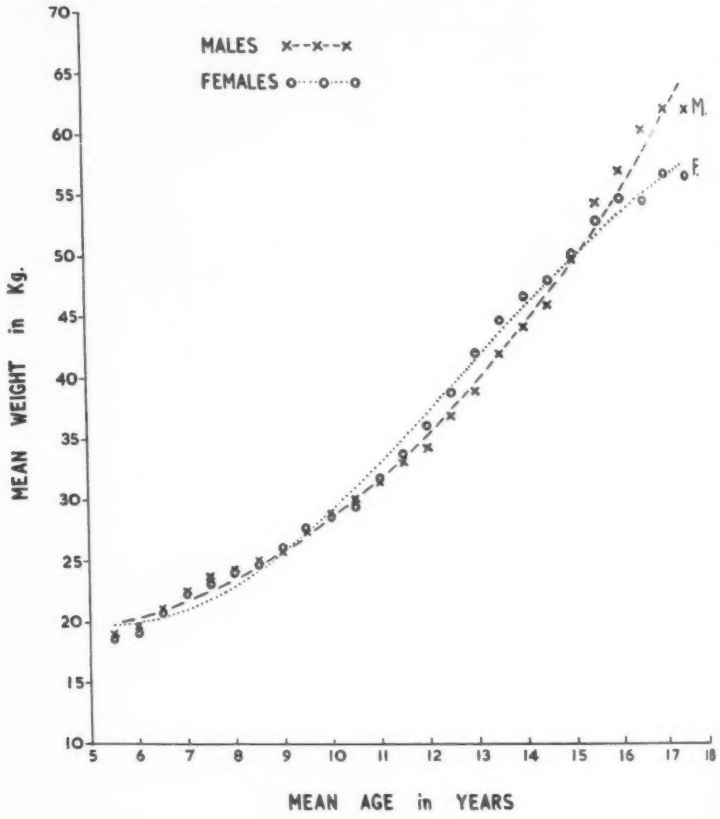

FIG. 7.—Stratified sample of Edinburgh schoolchildren. Mean weight, by age and sex.

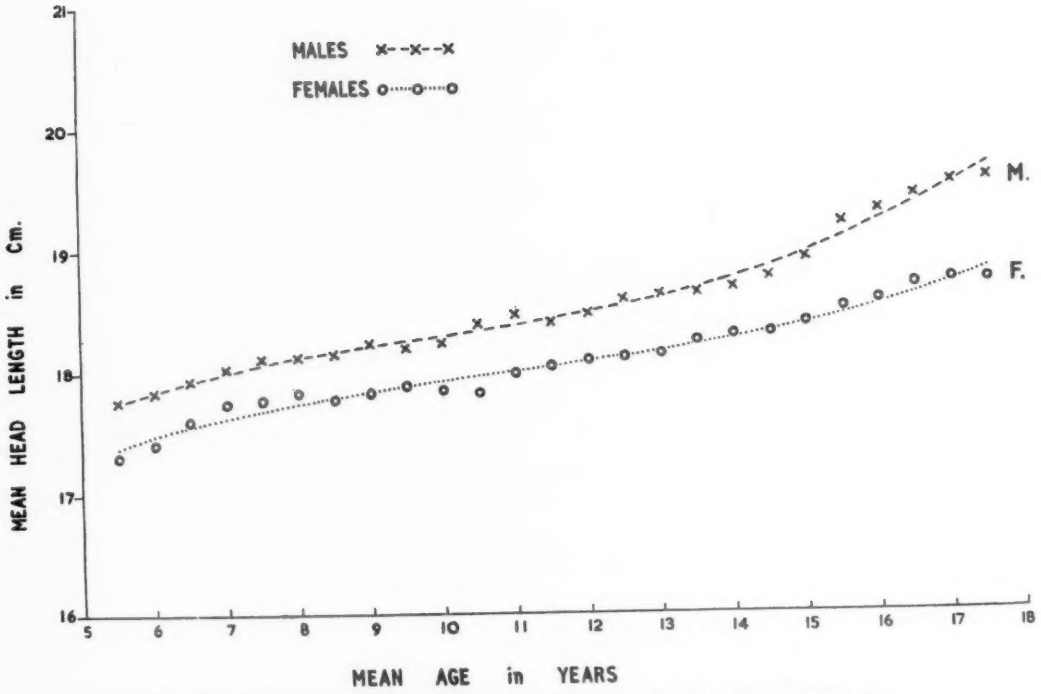

FIG. 8.—Stratified sample of Edinburgh schoolchildren. Mean head length, by age and sex.

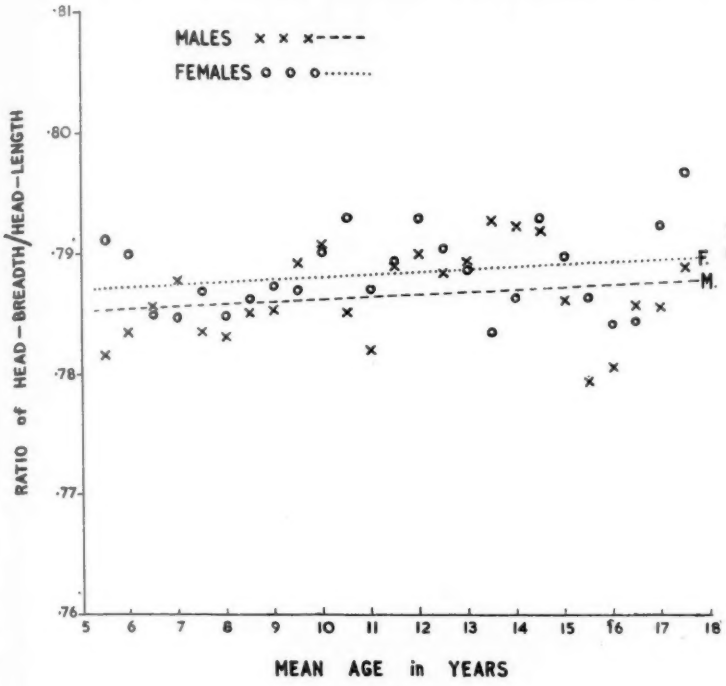

FIG. 9.—Stratified sample of Edinburgh schoolchildren. Relationship between head breadth and head length (cephalic index), by age and sex.

age-sex group; also drawn in Fig. 9 are the 'best-fitting' linear trends of mean cephalic index with age. (Though these lines give very poor summary descriptions of age-trends owing to the relatively wide and irregular scatter of the age-group means, no curve would give any better description.) It will be seen in Fig. 9 that both the male and the female summarizing trends gave a slight positive slope of mean cephalic index with age. On the whole the mean cephalic index for groups of girls was a little higher than for groups of boys.

It is possible that the fluctuations in mean cephalic index reflect lack of precision in measurement rather than age changes in the head-breadth/length relationship; it must be remembered that measurements were made to the nearest half-centimetre, using a Collins pelvimeter. The data obtained in this cross-sectional study cannot give inferences about longitudinal growth patterns. The linear trends, however, do not support the conclusion drawn by Cawley, Waterhouse and Hogben (1949) that the mean cephalic index decreases with age in a male population and that before the age of 12 years a female population is on the average more dolichocephalic than a male population.

Discussion

The results obtained in this investigation agree in the main with the findings of other investigators. But for certain characters, notably biacromial diameter and pelvic width, the findings in the present study are markedly different from those of Hogben, Waterhouse and Hogben (1948). In the latter study the mean biacromial widths for groups of boys were considerably lower than those found in groups of Edinburgh boys of similar age (differences ranging from $3\frac{1}{2}$ cm. at age $9\frac{1}{2}$ years to $5\frac{1}{4}$ cm. at $15\frac{1}{2}$); and the means for groups of girls were about 1 cm. lower than for Edinburgh girls of similar age. Moreover, the finding that 'the mean absolute shoulder width of the girl is greater than that of the male, and there is no sharp divergence associated with puberty' was not borne out in the Edinburgh results. Though there might be several explanations for the differences between the means recorded by Hogben *et al.* and those found in Edinburgh, the different male/female relationships cannot be easily explained. Even more markedly different are the findings of Hogben *et al.* in respect of pelvic width; their conclusion was that 'until the thirteenth year, there is no consistent difference between the mean pelvic width of the girls and boys of our sample. Thenceforward, in each age group, the absolute mean of the hip width of the female is greater than that of the male of the same age.' In the Edinburgh groups the mean pelvic width was greater for boys than for girls up to the age of $11\frac{1}{2}$ years; from 12 to $15\frac{1}{2}$ years the means for girls were greater than those for boys, but from 16 years and onwards the means for boys were again greater than those for girls.

These measurements are of course no guide to the pattern of growth of the individual child. Group means may and often do suggest a steady rate of growth from year to year, yet individuals within the group may be well below the average in one year and well above in the following year. Only longitudinal studies would provide the data to indicate how often a child of average weight or height at one age continues in succeeding years to be of average weight or height, and how often an individual child's growth fluctuates widely from above to below the group average year by year.

It is interesting to observe the similarity between the coefficients of variation of total length, stem length, span, biacromial diameter and pelvic width —a similarity not only in the magnitude of the coefficients of variation but in their age pattern. The much greater variability of weights of individual children and the more marked age trends in such variability are to be expected. By contrast, the low variability of head measurements and the lack of any age trend in variability is worthy of note; it is presumably attributable to the fact that most of the head growth has already occurred before the age of 5 years.

Two further points of interest seem worthy of comment. First, reference has already been made to the possibility that the measuring of female subjects by male investigators might be less consistent than the measuring of male subjects. This is a point to bear in mind when considering the irregularity in the pattern formed by the mean measurements of groups of girls; moreover, it might repay further investigation in future studies. Secondly, in analysing the data obtained in this study it was observed that all the measurements taken with the Collins pelvimeter (to the nearest half-centimetre) showed a marked bias for the whole-centimetre measurements as compared with the half-centimetre measurements. In the frequency distributions the whole-centimetre measurements were nearly four times as common as the half-centimetre measurements. Needless to say, corrections were made in the analysis to compensate for this bias; but future investigations might guard against the possibility of such bias.

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THE VALUE OF SPLENECTOMY IN FANCONI'S ANAEMIA

BY

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The syndrome described by Fanconi (1927), which consists of hypoplastic anaemia, multiple anatomical defects and pigmentation of the skin is now well recognized though uncommon; some 28 cases have been recorded.

This report is made with the object, not only of placing on record the features of two cases, but of examining the place of splenectomy in treatment. In nine instances splenectomy has now been performed and the results have been unsatisfactory. Opinions as to the value of operation and the indications for performing it differ, though it is generally agreed to be valueless if marrow hypoplasia is extreme.

Case Report

Dorothy M., aged 8 (born on June 13, 1944), was the only child of a second marriage. There were four children from previous marriages of her parents, and these children were all normal. There was no history of anaemia or congenital abnormality in any other member of the family. The parents of the child were healthy and their blood counts were normal.

She had always been well, apart from an attack of measles, followed by pneumonia, when she was aged 6. The parents denied that she was ever lacking in energy, and had not noticed that her appearance was in any way unusual. A month before admission, she had bled from the nose and throat for two days, and had been pale ever since.

On admission, the child was found to be very small. She weighed 32 lb. Her height was 3 ft. 6 in. and her skull circumference 17½ in. She was deeply pigmented all over, the colour being a dark, smoky brown. This was most marked on the abdomen and in the flexures, where there were patches of deeper pigmentation. Her eyes were very small, with a mongolian slant, and there was no strabismus. Her appearance was completely unlike that of any other member of the family. Her right thumb was extremely small, but fully functional. There was no other skeletal abnormality. Radiographs showed no changes in the skull, thoracic cage or long bones.

No abnormality could be found in the heart or lungs, and there was no lymphadenopathy, splenomegaly or hepatomegaly. There was no abnormality of the external urogenital system and the central nervous system appeared normal.

Investigations. A full blood count gave: haemoglobin, 37% (5·4 g. %); red blood cells, 1·52 million; colour index, 1·23; white blood cells 6,400 (polymorphs 29%, lymphocytes 66%, monocytes 3%, basophils 2%, reticulocytes 4·4%). Red blood cells showed anisocytosis and poikilocytosis. Cells were fully haemoglobinized. There were no spherocytes, target cells or sickle cells.

FIG. 1.—Photograph of Case 1 showing micro-ophthalmos, microcephaly and pigmentation.

Haemolysis was incomplete at 0·45%, complete at 0·3%. The direct Coombs test was negative and no warm or cold agglutinins were detected by Dacie's method. The erythrocyte sedimentation rate was 51 mm. in one hour, the bleeding time 7 minutes 30 seconds, clotting time 2 minutes 30 seconds, platelets 50,000 per c.mm.

Marrow examination gave total cells 9,000 (neutrophils, segmented 8·0%, unsegmented 2·0%, metamyelocytes 3·0%, myelocytes 3·5%, promyelocytes 0·5%,

eosinophils 0·5%; smear cells and naked nuclei 11·5%, lymphocytes 43·0%, monocytes 2·5%, promonocytes 0·5%. Normoblasts: late, 4·0%; intermediate, 12·0%; early, 8·5%. Total: 24·5%. Cells in mitosis, 0·5%. Myeloid-erythroid ratio, 0·7 : 1.

The low total nuclear count and the high proportion of lymphocytes indicated greatly depressed marrow activity, and the low myeloid-erythroid ratio that myeloid activity was at a very low ebb indeed. There were no abnormal cell types.

delayed. The shadow of the right kidney was seen to overlie the left sacro-iliac joint. No excretion could be seen anywhere on the right side.

Serum electrolytes were normal. The sterone and 17-ketosteroid content of the urine was within normal limits. There was no steatorrhoea.

Although the child appeared well, after two weeks the white cells dropped to 1,600 (polymorphs 31%, lymphocytes 66%, monocytes 3%). Platelets fell to 17,000 and the bleeding time rose to 8½ minutes. She developed

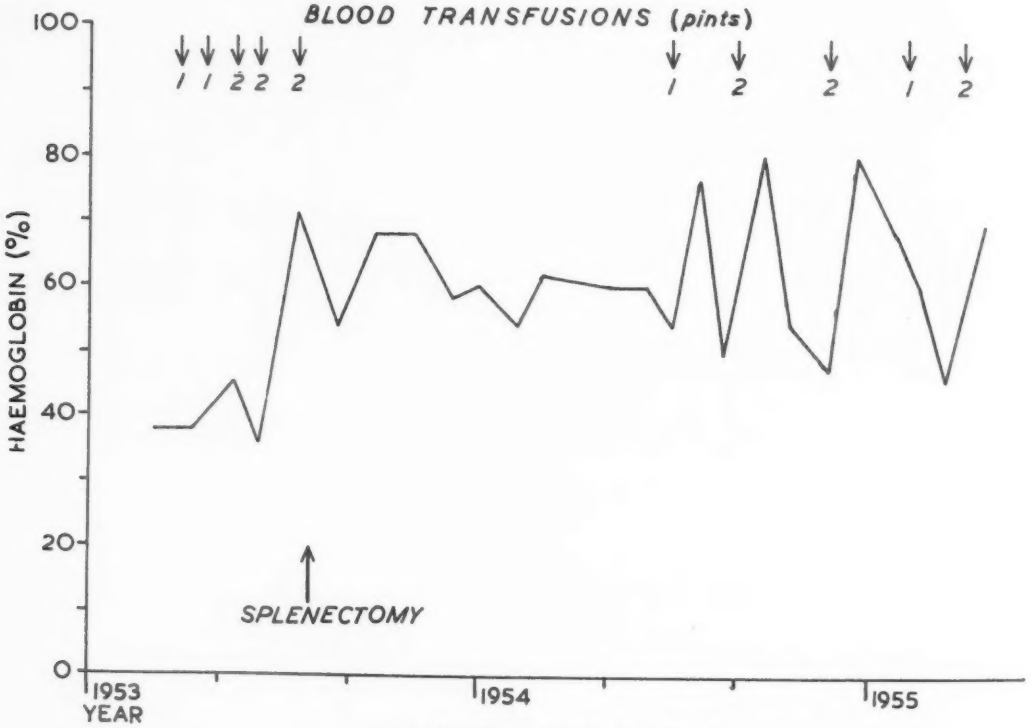

FIG. 2.—Haemoglobin levels in Case 1.

The blood urea level was 31·3 mg. %, and the serum cholesterol 310 mg. %. The direct Van den Bergh test was negative, the indirect within normal limits. Thymol turbidity was 4 units and zinc sulphate turbidity 2 units. The colloidal gold test was negative.

Urine. There was a faint trace of albumin, no reducing substances, bile pigments or salts. Urobilinogen was absent and there was no phosphaturia, cystinuria or tyrosinuria. Microscopy revealed no abnormality and culture was sterile.

The stools were frequently examined, and were always negative for occult blood.

Section of skin showed an increased amount of pigment in the cells of the basal and prickle layers of the epidermis. There was a large proportion of pigment containing macrophages in the corium, just under the epidermis.

An intravenous pyelogram showed that excretion was

patches of purpura on the arms, abdomen and legs, and vomited bloodstained mucus. Following transfusion her blood picture continued to deteriorate and necessitated frequent further transfusions. She developed epistaxis, and one attack of acute abdominal pain, after which her stools contained occult blood. A course of cortisone was tried, but had no effect whatever on haemopoiesis. A further bone marrow examination three months later showed a marked increase in erythroblastic activity compared with the previous examination. Myeloid activity was still reduced. Frequent reticulocyte counts showed a variation between 1·2% and 6·8%. In view of the low bone marrow activity, and the fact that the child was needing transfusions every three weeks, it was decided to undertake splenectomy.

The operation was performed on July 21, 1953, by Mr. Stanley. A normal-sized spleen was removed with ease.

Section of the spleen showed well developed lymph follicles with active germ centres. The pulp was highly cellular, with prominent sinuses in which the littoral cells were hyperplastic. Free and phagocytosed blood-pigment was plentiful. There was no erythroid hyperplasia and no erythrophagocytosis.

During the week preceding the operation the patient was given 1 pint of blood and 1 pint of packed red cells. Immediately after the operation the blood count was:

Red blood cells 2,640,000, haemoglobin 65%, white blood cells 1,200 (lymphocytes 40%, polymorphs 57%, eosinophils 1%, monocytes 2%, reticulocytes 3%).

This picture gradually improved without further treatment, until one month after the operation, when the blood picture was: Red blood cells 3,040,000, haemoglobin 68%, white blood cells 3,200, lymphocytes 60%, polymorphs 39%, monocytes 1%.

Her blood picture from then on varied as shown on the graph, but nine months after the operation the red cell count had fallen to 1,670,000. She had remained asymptomatic during this period. She was re-admitted and transfused with 1 pint of whole blood. Three months later she was re-admitted with pain in the back and high pyrexia. The blood count was then: red cells 2,400,000 and haemoglobin 48%.

There was marked bruising of both legs, but the condition settled down after further transfusions. She has needed further transfusions at diminishing intervals.

Case 2. Ian L., aged 5 (born on November 29, 1948), was an only child. He had had the common exanthemata mildly, but had otherwise been in good health until three months before admission when recurrent epistaxis had developed.

The mother and father were well and there had been no other pregnancies. There was no consanguinity and no knowledge of any condition resembling that of our patient in the family (two cousins, two aunts, one uncle, five in the grandparent's and three in the great grandparent's generations). One maternal second cousin is said to have died at the age of 18 but the cause was not known. The only abnormality found in the parents was in the father who had an area of vitiligo measuring 2 in. × 1 in. over the epigastrium. Their blood counts were normal.

The boy was admitted to hospital on October 10, 1953, on account of a profuse epistaxis following a head cold. The haemoglobin had fallen to 3·3 g. per 100 ml. (22%) and an immediate transfusion of 2 pints (1·3 litres) of whole blood was given. The only other haemorrhagic manifestation was bruising over the left tibia which may well have been traumatic in origin.

He was a small child for his age with an immature appearance and fair complexion. His height was 3 ft. 2 in. (96·6 cm.), weight 27 lb. (12·2 kg.), skull circumference 19½ in. (52·5 cm.). Weight was 4 lb. 2 oz. at birth (one month premature).

Areas of light brown pigmentation were present on the right cheek and abdomen and a clearly defined area of depigmentation on the epigastrium.

The right wrist was in valgus deformity and the corresponding thumb absent. The left upper limb was normal except for a small but fully functional thumb.

Radiologically the right first rib and humerus were narrower than those on the left. The right radius was shortened with malformed and rounded metaphyses. The right ulna showed a similar deformity and in addition

FIG. 3.—Areas of pigmentation and depigmentation in Case 2.

curvature of its shaft, greatest about one inch below the head. Neither lower epiphysis was visible. Two ossification centres were present in each carpus but none to indicate skeletal rudiments of a right thumb. The metacarpal and phalangeal bones of the right were narrower than those of the left hand.

FIG. 4.—Deformity of forearms and hands in Case 2.

Over the precordium and loudest in the third left interspace a rough systolic murmur was audible, but unaccompanied by any alteration in the intensity or quality of the heart sounds or abnormality in shape or size of the heart. Blood pressure was 100/70 mm. Hg.

Examination of the ocular, nervous, external urogenital and respiratory systems was negative. His intelligence, though not formally estimated, was considered normal for his age.

Investigations. A blood count on December 10, 1953, gave the following results: Red blood cells 2,500,000 per c.mm., cells showing anisocytosis and polychromasia, haemoglobin 8·5 g./100 ml., colour index 1·2, P.C.V. 24%, reticulocytes 0·8%, white blood cells 3,000 per c.mm. (neutrophils 1,440, monocytes 120, lymphocytes 1,440). E.S.R. (Westergren) 25 mm./hr., platelets 47,000 per c.mm., bleeding time 5 minutes, clotting time 5-9 minutes, prothrombin time 14 sec. (control 14 sec.).

A total nucleated count of the tibial marrow on November 13 was 5,000:

Leukoblasts	0·5%	59·5%
Promyelocytes	0	
Myelocytes	11·5	
Metamyelocytes	12	
Neutrophil	33·5	
Eosinophil	2·0	
Lymphocytes	6·5%	
Proerythroblasts	1	34%
Early normoblasts	3·5	
Intermediate normoblasts	15·5	
Late normoblasts	14	

Megakaryocytes were very scanty.

On an intravenous pyelogram the position and shape of the right kidney and ureter were normal. The left ureter was visualized only in the pelvis and no renal shadow was seen, indicating that this kidney was functional but displaced downwards and overlying the sacro-iliac joint.

An analysis of the urine showed: Albumin 15 mg. %, reducing substances nil, a few R.B.C.s only and no casts.

A serum protein estimation gave: albumin 4·5 g. %, globulin 2·0 g. %, fibrinogen 0·3 g. %.

Serum cholesterol was 155 mg. %.

His clinical condition improved satisfactorily after the initial transfusion. The haemoglobin concentration, however, was not maintained and fell steadily for six weeks. After this there was a period of spontaneous improvement in the haemoglobin, leucocytes and platelets, though at no time was any significant reticulocytosis found. Immediately before his second major epistaxis there were again indications of haematological relapse. In the intermediate phase the only incidents were minor epistaxes and on one occasion brisk haematuria. The second major epistaxis was associated with coryza and was so severe that he was *in extremis* from exsanguination although arrangements for immediate admission and transfusion had previously been made for just this emergency.

It was decided, therefore, that splenectomy should be undertaken since no other form of treatment offered any protection against haemorrhage.

The operation was carried out on March 10, 1954, by Mr. Laurenson and proceeded uneventfully. On removal the spleen appeared normal and was of normal size.

On the second post-operative day the platelet count rose to 152,000, but thereafter fell rapidly to 70,000.

On the fourth day he began to vomit and this persisted in spite of treatment. Two days later he had repeated haematemeses and his condition deteriorated. He died on the ninth post-operative day.

Post-mortem Examination. The heart was of normal size for his age (weight 70 g.) and no congenital or other abnormality was identified in it or the great vessels.

Patchy haemorrhagic bronchopneumonia was present in the lower lobes of both lungs. Microscopically there was much extravasation of red cells into the alveolar exudate. The air passages and pleural surfaces were normal.

The stomach, duodenum, jejunum and ileum were greatly dilated, the ileum being three times its normal diameter. There was no evidence of excessive bleeding in the region of the operation.

The liver was normal in size (weight 430 g.), but pale on section, microscopically showing fatty change. The gall bladder and pancreas were normal.

The right kidney (weight 40 g.) was normal in position, orientation and blood supply. The left kidney (weight 35 g.) was normal in size and appearance, but was situated on the pelvic brim 2·5 cm. below the aortic bifurcation. The renal artery on this side arose at the bifurcation and the renal vein emptied into the common iliac vein. The kidney was rotated with its pelvis lying anteriorly. The ureter, which was naturally short, descended anteriorly to enter the bladder in the normal position. The bladder and genitalia were normal.

The adrenal glands were present in the usual site and were histologically normal.

The skull, meninges, basal arteries, brain, ventricular system and the venous sinuses were normal for a boy of his age.

The lymph nodes were normal.

Discussion

The conditions of the children whose cases are described fulfil the diagnostic criteria necessary for classification as examples of the syndrome described by Fanconi (1927) in that they showed hypoplastic anaemia, skeletal deformities and abnormal pigmentation.

Haemorrhages and anaemia were the presenting and outstanding symptoms and were the features which governed management. Although the bleeding and clotting times remained normal the platelet counts were invariably diminished. Moreover, the megakaryocytes were so reduced in number that differential counts were not practicable. The erythrocytes were macrocytic with marked anisocytosis and polychromasia. On no occasion was the reticulocyte count found to be raised in Case 2, but in Case 1 a reticulocytosis varying between 1·8% and 6·8% was present. There was no erythroid hyperplasia in Case 2, nor in the first examination in Case 1. The second examination

in Case 1, however, showed evidence of erythroid activity. Evidence of haemolysis *in vivo*, as judged by splenomegaly, reticulocytosis and raised serum bilirubin, was lacking. It was, nevertheless, decided to carry out splenectomy since the bone marrow was merely hypoplastic as judged by the specimens taken and not completely aplastic—a difference in degree which is held to be important in determining the effect of splenectomy (Reinhold, Newmark, Lightwood and Carter, 1952). In their patient on whom splenectomy was carried out, there was no initial reticulocytosis nor erythroblastic hyperplasia and it was thought that hypersplenism might be a factor, but after operation improvement was not maintained.

The patients reported by Dacie and Gilpin (1944) remained well after splenectomy, though the authors were cautious in concluding that the remission could with certainty be attributed to the operation. In their case there was evidence of excessive haemolysis in that rapid auto-haemolysis was observed *in vitro*; in addition there was a reticulocytosis and the marrow showed erythroblastic hyperplasia.

The case reported by Estren, Suess and Dameshek (1947) was also benefited at least temporarily by splenectomy. In this instance there was a significant reticulocytosis ranging from 2% to 11% before operation and improvement, though small, was maintained for two months, beyond which time no findings are reported.

Rohr's (1949) case, which was not benefited by operation, had no reticulocytosis and very few megakaryocytes in the bone marrow. The marrow picture, however, was not typical of aplastic anaemia because plasmocytes, mast cells and fibrocytes predominated. The blood picture was also unusual because the osmotic fragility of the red cells was increased, and it is therefore doubtful if his case falls into the category described by Fanconi.

The case reported by Silver, Blair and Kempe (1952) had no reticulocytosis at the time of operation and no improvement followed in either platelet count or the haemorrhagic tendency.

The experience of Estren and Dameshek (1947), in successfully abolishing the haemorrhagic tendency in a child suffering from familial hypoplastic anaemia not of the Fanconi type by removal of the spleen, is of interest and relevant to the present discussion. The reticulocyte count, which was initially elevated, fell to normal after operation, the erythrocyte count increased from 1,380,000 to 2,450,000 per c.mm., the haemoglobin from 4 to 9·8 g., the leucocyte count from 1,800 to 2,400 per c.mm., and the platelet count from 4,140 to 113,000 per c.mm. They found that megakaryocytes were normal in number but showed little platelet formation.

Two further cases which have undergone splenectomy without improvement are recorded, but as full details are not given (Diamond, Smith and Vaughan, 1954; van Leeuwen, 1933), they are not discussed here.

It is thus apparent from consideration of these patients on whom splenectomy has been performed that the degree of hypoplasia judged by examination of the marrow is insufficient evidence upon which to differentiate suitable from unsuitable cases.

Only two of the seven patients with Fanconi's syndrome improved after operation; these patients differed from the remainder in having significant and persistent reticulocytoses until the time of operation and bone marrow showing erythroid hyperplasia. On the other hand, in those who were not benefited the reticulocyte count was normal or low at the time of operation. The cellularity and quality of the marrow in respect of leucocyte and platelet precursors and the degree of polychromasia in the blood did not bear any apparent relationship to the outcome of the operation.

The reticulocytosis in the successful cases was attributed in one to haemolysis (Dacie and Gilpin), but in the other (Estren, Suess and Dameshek, 1947) haemolysis was not demonstrable. In neither of the present cases was there any evidence of haemolysis and the presence of a mild reticulocytosis in Case 1 implies that the reticulocytosis was a manifestation of regenerative activity of the marrow in response to the stimulus of anaemia. It may therefore be taken as a measure of total (erythroid) marrow output, irrespective of local variations in activity of the marrow from bone to bone. A reticulocyte count that is normal or low by accepted standards is thus a demonstration of total (erythroid) marrow insufficiency, which precludes any increase in the erythrocyte count following splenectomy.

As the condition runs its course, progressively or with remissions, the reticulocyte response diminishes (Silver *et al.*, 1952) *pari passu* with diminishing erythroblastic activity, and the erythrocyte count can no longer be maintained. In our Case 1 there was apparent improvement following splenectomy, but this was not maintained and it could be argued that this was but part of the natural history of the disease rather than a response to splenectomy.

The benefit after splenectomy is therefore at best temporary and cannot be attributed to correction of the basic defect. In patients who are improved the effect may last for several months, and the benefit persist longer than that following transfusion; at the same time the need for transfusion

is postponed. It is debatable, however, whether the inconvenience and risk of operation even in suitable cases are warranted by this advantage, which, with the modern techniques and safety of transfusion, is small.

Since other forms of treatment, such as liver extracts, folic acid, iron compounds and cortisone, are without effect, reliance should be placed on repeated blood transfusions as the mainstay of therapy.

Summary

The clinical and haematological findings in two children suffering from Fanconi's syndrome are described.

The indications for splenectomy as a method of treatment for this condition are considered.

Splenectomy may be beneficial in those cases with evidence of regenerative activity as demonstrated by the presence of erythroid hyperplasia of the bone marrow and reticulocytosis in the blood. The benefit is short-lived.

Splenectomy brings no improvement in those cases which show no evidence of regenerative activity and in which the reticulocyte count is not raised.

We acknowledge with thanks the assistance of our colleagues, Dr. E. C. Dawson and Dr. Keith Randall, and Dr. J. Dales, for carrying out the haematological examinations.

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THE VITAL CAPACITY OF CHILDREN

BY

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In 1846 Hutchinson published an exhaustive treatise on pulmonary function, giving an historical review and describing in detail methods for measuring pulmonary ventilation using, apparently for the first time, a spirometer. Most investigators since then have followed Hutchinson's lead and used spirometers to record their measurements.

The following simple methods of measurement have been those generally used: (1) Vital capacity, which is determined by measuring the maximum amount of air exhaled after a full inspiration; (2) maximum breathing capacity, which is a measurement of the greatest amount of air that can be moved in and out of the chest in a given period of time.

Figures for normal values in adults have been published, but few for children are available. Such figures for American children have been given by Emerson and Green (1921) in a group of boys aged 8 to 15 years and in girls from 7 to 13 years, by Wilson and Edwards (1921) in 85 normal children, 44 boys and 41 girls aged from 6 to 16 years and by Ferris, Whittenberger and Gallagher (1952) in 161 boys aged 5 to 18 years. Robinson (1938) includes recordings for about 20 healthy boys in a detailed study of the relation of physical fitness to age. The only article found dealing with British children is that by Moore and Gibson-Williams (1951), who measured the vital capacity and maximum breathing capacity in 152 healthy boys from 10 to 15½ years of age.

The recording of such normal values in children presents certain difficulties, notably the impossibility of being certain that a young child is trying his best. For this reason it is necessary to take measurements in a large group of healthy children, to win their confidence by careful explanation of what is required of them and to see that they are not intimidated by the apparatus. Children under 6 years old were found to be too unreliable in their efforts to make their inclusion worthwhile.

In an attempt to provide a set of normal measurements which might be of value, this study was undertaken. Healthy children of both sexes aged 6 to 13½ years had their vital capacities measured. The maximum breathing capacity was not estimated as the procedure necessary was found to be inaccurate in the younger children, many of whom were unable to maintain the necessary effort for the time required, and it was felt desirable to use a method simple enough to be undertaken in any small hospital physiotherapy department.

Method

To obtain figures for normal children, patients attending hospital were not used, as many of these suffer from conditions likely to affect pulmonary efficiency and others will have been ill and therefore inactive, with a resulting fall in capacity. To obviate this difficulty, a list of Wolverhampton school children between the ages of 6 and 13½ years was kindly supplied by Dr. B. Sergeant, senior assistant school medical officer of Wolverhampton. Care was taken to see that the list contained children of all social grades and those chosen were not confined to one school, so that pupils from housing estates on the periphery of the town as well as those from the more crowded centre were included. Letters were sent to the parents of those selected inviting them to attend and stating the purpose for which they were being examined. They were informed that no treatment would be given. More than half of those invited attended, and after discarding a number either on account of some illness or because full cooperation was not obtained, measurements were made on 324 boys and 301 girls. On arrival, a history was taken from the parent, and the child was examined clinically. Those found to be suffering from any (usually respiratory) disease were excluded.

After explaining to the children what was required of of them, heights and weights were recorded while wearing only pants and socks. The chest expansion was then measured and finally the child sat on a stool in front of a Benedict-Roth type of spirometer. Each child was given a clean glass mouth-piece attached to the rubber inlet tube of the instrument and was shown what happened when he blew into the mouth-piece. He was encouraged to inspire as fully as possible and then expire to his maximum ability through the mouth-piece. After a preliminary trial, three such attempts were made and recorded without hurrying the child. It was

intended to repeat the procedure with the child lying semi-recumbent on a couch, but as it was found in nearly all cases that the figures obtained in the sitting position were greater, the recumbent posture was discarded and a fourth attempt in the sitting position was made. There is no doubt that a number of the subjects might have improved on their results by further practice, as was shown in the boys of Moore and Gibson-Williams (1951), who found a mean increase of 2·8% in the vital capacities on repeating the tests after an interval of six weeks. This improvement with practice must be remembered when serial determinations are made. In this series, the method described above was adhered to rigidly to try to achieve a constant result in the simplest manner possible, and, in fact, the fourth attempt rarely bettered the third.

Measurements have been recorded in centimetres for height and kilograms for weight and the surface areas have been calculated from the heights and weights using the nomogram in Du Bois' (1936) book.

Results

Vital capacity is not accurately correlated to age, height and weight as noted by Dreyer (1920), who found a relationship to exist between certain body measurements, weight, chest circumference and stem-length, and published tables (Dreyer, 1919). In adults, West (1920) showed that vital capacity had a much closer relationship to the body surface area than with age, height or weight, although it tends to rise more uniformly with increasing height than with weight (Baldwin, Cournand and Richards, 1948).

As regards children, Wilson and Edwards (1921) found in 44 boys, 6 to 16 years old, an average vital capacity of 1,902 ml. for each square metre of body surface and 1,837 ml. for 41 girls of the same age for the same area. Emerson and Green (1921) gave

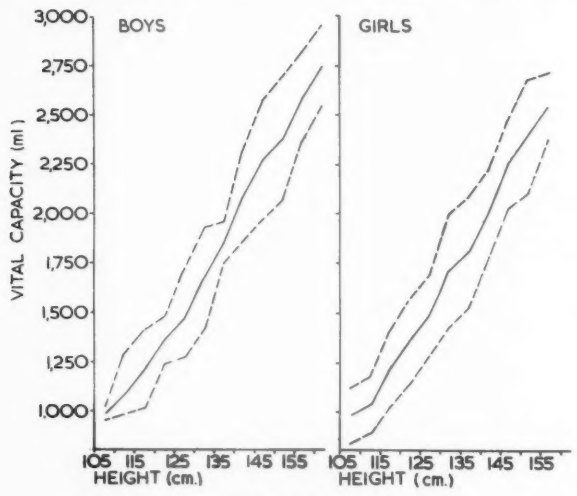

FIG. 1.—Vital capacity—height in boys and girls.

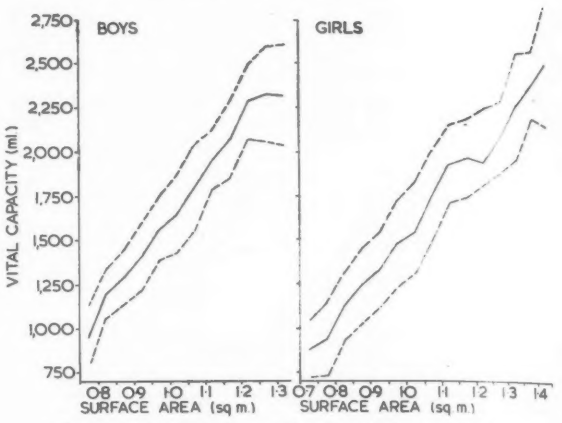

FIG. 2.—Vital capacity—surface area in boys and girls.

rather different figures for boys in four groups based on height, varying from 1,800 ml. for a surface area of 1·5 square metres to 800 ml. for a surface area of 1 square metre, which is considerably different. Moore and Gibson-Williams (1951) gave figures for 152 boys aged from 10 to 15½ years and used both vital capacity and maximum breathing capacity in their researches. For vital capacity they conclude that this was best recorded by the formula:

Vital capacity (ml.) = 2,235 + 90·8 (age—13·114)

with 95% limits approximately ± 480 ml. for all calculated values.

This last appears to be the only British contribution to the subject as applied to children in recent years. Whitfield, Waterhouse and Arnott (1950) advised the use of four physical attributes: age, height, weight and surface area, for, while any one of these may be effective for an individual who is normal in every respect, this will not be the case

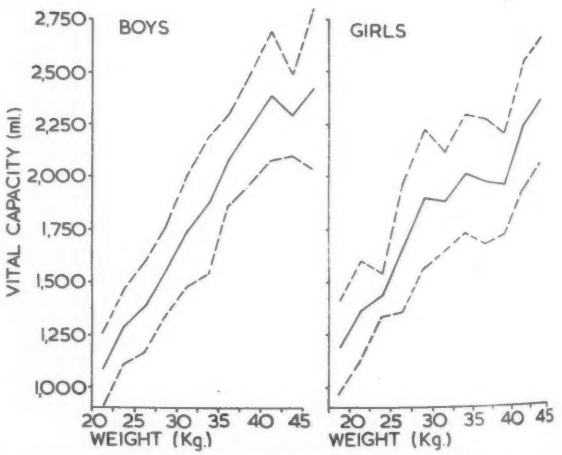

FIG. 3.—Vital capacity—weight in boys and girls.

VITAL CAPACITY—WEIGHT IN BOYS AND GIRLS

Group (kg.)	Boys			Girls		
	No. of Cases	Mean (ml.)	Standard Deviation (ml.)	No. of Cases	Mean (ml.)	Standard Deviation (ml.)
17·5–19·9	18	1,075	177	—	—	—
20 –22·4	47	1,281	180	48	1,185	224
22·5–24·9	46	1,378	218	55	1,361	238
25 –27·4	34	1,547	211	31	1,437	103
27·5–29·9	50	1,737	262	42	1,664	311
30 –32·4	24	1,862	322	17	1,899	332
32·5–34·9	28	2,077	220	26	1,885	238
35 –37·4	17	2,229	258	15	2,016	283
37·5–39·9	16	2,380	306	10	1,979	299
40 –42·4	14	2,290	195	10	1,967	242
42·5–44·9	12	2,416	380	10	2,241	303
45 –47·4	—	—	—	7	2,364	298
47·5–49·9	—	—	—	5	2,343	313

VITAL CAPACITY—HEIGHT IN BOYS AND GIRLS

Group (cm.)	Boys			Girls		
	No. of Cases	Mean (ml.)	Standard Deviation (ml.)	No. of Cases	Mean (ml.)	Standard Deviation (ml.)
105–109·9	4	987	37	7	892	143
110–114·9	14	1,078	220	16	946	145
115–119·9	35	1,211	197	23	1,134	194
120–124·9	37	1,353	121	54	1,276	213
125–129·9	49	1,466	240	40	1,403	205
130–134·9	46	1,666	258	30	1,629	288
135–139·9	37	1,848	103	44	1,723	277
140–144·9	35	2,085	226	28	1,921	222
145–149·9	22	2,269	301	18	2,171	226
150–154·9	18	2,379	313	14	2,313	289
155–159·9	8	2,586	232	8	2,460	172
160–164·9	5	2,744	207	—	—	—

VITAL CAPACITY—AGE IN BOYS AND GIRLS

Age Group (years)	Boys			Girls		
	No. of Cases	Mean (ml.)	Standard Deviation (ml.)	No. of Cases	Mean (ml.)	Standard Deviation (ml.)
6 – 6½	19	1,138	183	15	926	195
6½– 7	23	1,218	210	20	1,022	147
7 – 7½	17	1,248	190	15	1,162	152
7½– 8	27	1,313	193	29	1,218	255
8 – 8½	29	1,408	249	29	1,345	295
8½– 9	32	1,527	200	28	1,453	186
9 – 9½	27	1,603	254	28	1,520	231
9½–10	26	1,797	321	26	1,656	336
10 –10½	19	1,862	253	15	1,661	280
10½–11	14	1,909	273	15	1,864	265
11 –11½	23	2,104	252	17	2,006	299
11½–12	19	2,134	292	15	1,838	290
12 –12½	20	2,270	372	17	2,087	265
12½–13	13	2,122	327	20	2,275	313
13 –13½	16	2,521	240	12	2,357	246

VITAL CAPACITY—SURFACE AREA IN BOYS AND GIRLS

Group (sq. m.)	Boys			Girls		
	No. of Cases	Mean (ml.)	Standard Deviation (ml.)	No. of Cases	Mean (ml.)	Standard Deviation (ml.)
0·70–0·74	—	—	—	10	876	160
0·75–0·79	10	942	180	16	929	208
0·80–0·84	27	1,193	138	20	1,113	188
0·85–0·89	47	1,289	154	33	1,234	207
0·90–0·94	37	1,407	192	40	1,322	208
0·95–0·99	28	1,567	181	30	1,467	244
1·00–1·04	37	1,652	218	27	1,534	232
1·05–1·09	33	1,808	247	25	1,744	248
1·10–1·14	19	1,963	169	20	1,924	217
1·15–1·19	25	2,079	218	21	1,959	219
1·20–1·24	16	2,292	212	13	1,932	302
1·25–1·29	19	2,334	271	11	2,075	202
1·30–1·34	10	2,328	284	11	2,258	305
1·35–1·39	—	—	—	6	2,380	191
1·40–1·44	—	—	—	9	2,503	353
1·45–1·49	—	—	—	5	2,565	164

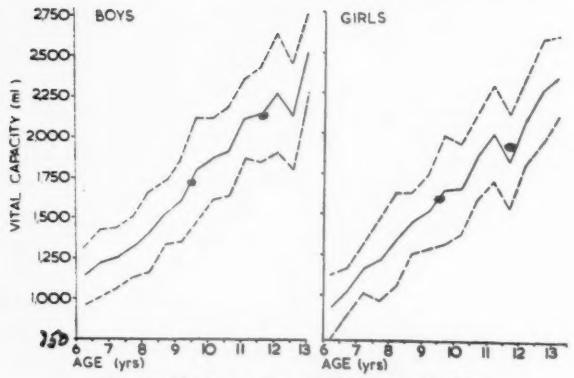

FIG. 4—Vital capacity—age in boys and girls.

for anyone who is, say, short and fat. In such a person prediction by height is likely to give a reading too low, while one by weight will probably forecast too high a result.

In view of the findings of the workers mentioned above, separate tables have been prepared for age, height, weight and surface area for both sexes. The tables for age are divided into groups of six months, those for height into increments of 5 cm., those for weight into divisions of 2·5 kg., and those for surface area into sections each increasing by 0·05 square metres of body surface. The number of children recorded in the groups for height, weight and surface area tend to be slightly less than the totals for age, as a number, too small to be significant, fell outside the ranges given.

Curves are also given for the mean values (solid lines) and standard deviation ranges, above and below the means (dotted lines). It will be noticed that the most smoothly rising curve in each sex is that recording vital capacity for height, which corroborates the findings of Baldwin *et al.* (1948). The standard deviations will be seen to be rather large, though on the whole less than the somewhat comparable figures given for boys by Ferris *et al.* (1952), probably because the numbers in the groups of the latter are less. The most likely explanation for this is failure of some of the subjects to cooperate fully in the tests. Wilson and Edwards (1921) also noted this and, while agreeing that the human error was chiefly responsible, they felt that some other factor was at work and suggested that perhaps enlargement of the tracheo-bronchial lymph nodes might play a part. This has not been confirmed.

While examining patients who had a past history of pneumonia, a clinical impression was formed that their vital capacities were lower than normal, so to settle this point, a group of 85 children, 42 boys and 43 girls, who had a history of pneumonia in the past, was examined. The vital capacities of these children, who were healthy at the time of examination, were recorded for age, height, weight and surface area, and only if the figures in at least three out of the four readings for each child were below the mean minus the standard deviation were they accepted as abnormal. It was found that in only eight (three boys and five girls) was this the case. In five children (three boys and two girls), the vital capacities were above the mean plus the standard deviation. In those, eight of each sex, who had experienced two or more attacks of pneumonia, two fell into each of the above categories. There appears, therefore, to be no evidence that children who have had pneumonia have lower vital capacities than those who have not.

Summary

Values for the normal range of vital capacity for 324 boys and 301 girls aged from 6 to 13½ years are given.

No evidence has been found that children who have suffered from pneumonia have a lower vital capacity than those who have not.

I should like to express my thanks for the help given by the staff of the School of Physiotherapy at the Royal Hospital, Wolverhampton, in recording these measurements, and to Dr. K. W. Cross, Statistical Officer to the Birmingham Regional Hospital Board, for his statistical assistance.

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PREMATURE LOSS OF DECIDUOUS TEETH

BY

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Premature exfoliation of deciduous teeth is very rare in children. It is well known that it may occur in severe pink disease (acrodynia) and in local disease of bone, such as osteitis and eosinophilic granuloma (Thoma, 1937; Stones, 1954). The teeth in the above conditions are extruded with the roots intact due to a loss of their supporting bony tissue. In hereditary ectodermal dysplasia teeth are badly formed or lacking.

An extensive search of the literature, including all volumes of the *Quarterly Cumulative Index Medicus*, has failed to reveal more than two references to premature loss of deciduous teeth due to a cause other than the above. Sobel, Clark, Fox and Robinow (1953) described a child with genu valgum and premature loss of teeth. She was first seen at the age of 19 months. Six weeks previously several teeth had become loose and all had been shed before her first attendance at hospital. Her serum calcium and phosphorus levels were normal, but her serum alkaline phosphatase was low (0·9 to 1·64 Bessey-Lowry units). Biopsy of the liver and ribs showed a deficiency of phosphatase. Examination of the bone (by Dr. Edwards Park) showed a picture indistinguishable from that of rickets. There was no history of poisoning by beryllium, which interferes with phosphatase activity, or by fluoride. Radiographs of her limbs were thought to show an osteodystrophy. The tibiae were bowed, and there was cortical new bone formation, with irregular calcification in the metaphyses. The father's alkaline phosphatase was abnormally low, suggesting that the condition was of genetic origin. Treatment with 500,000 units of vitamin D for 10 days had no effect on the enzyme activity. The writers suggested that growing bone requires the presence of alkaline phosphatase for normal calcification, and that the skeletal disorder may be related to an abnormality in the quantity of phosphatase in the tissues.

This patient has been described by Sobel elsewhere, and Clausen (1952), in discussing the case, said that he had seen three similar children in one family.

Rathbun (1948) had previously described a case of osteodystrophy with a virtual absence of serum alkaline phosphatase, the figures ranging from 0 to 0·7 Bessey-Lowry units, but the child died before teeth erupted. Luder (1954) described a similar child, but in his case the serum calcium was high (14·8 mg. per 100 ml.) and the blood urea was raised (50-80 mg. per 100 ml.). The teeth (personal communication) were unaffected.

Below is the case history of a child with premature loss of deciduous teeth. He was referred to the Children's Hospital, Sheffield, by Dr. J. H. D. Millar of Scunthorpe.

Case History

The boy was first seen at the age of 2 years and 5 months, because his teeth were falling out and he had genu valgum. He was an only child, weighing 28 lb. His birth weight was 9 lb. His mother was well during pregnancy, and had had a good diet.

The boy was breast fed for the first week, then had National dried milk for two months, and finally 'ostermilk No. 2', until at 4 months he was given thickened feeds. He was given 20 drops of 'adexolin' daily from the age of 5 months. At 6 months he was given solids, and thereafter took a good diet, including adequate quantities of meat, eggs, fish and milk.

His development was normal. He sat without support at 6 months, walked without support at 11 months, said single words with meaning before his first birthday and put many words together before he was 2. Physically the boy was well, apart from the two symptoms for which he was referred to us. He was full of energy, happy and free from lassitude. The genu valgum was noted at the age of 20 months. There were no previous illnesses.

The two first lower incisors erupted at 3 months of age, and two more appeared in the ensuing two months, but they all became loose one to two weeks after their eruption. By the age of 5 months two of the lower deciduous incisors had exfoliated. During the following two and a half years, 11 further deciduous teeth were shed, until

FIG. 1.—View of the patient's upper teeth showing the narrow, high-vaulted palate.

FIG. 2.—Patient's dentition at 3 years of age after shedding 13 deciduous (milk) teeth.

FIG. 3.—Patient's lower deciduous molar (B) showing complete absorption of the roots. As a comparison (A) is a similar molar from a normal child of about the same age.

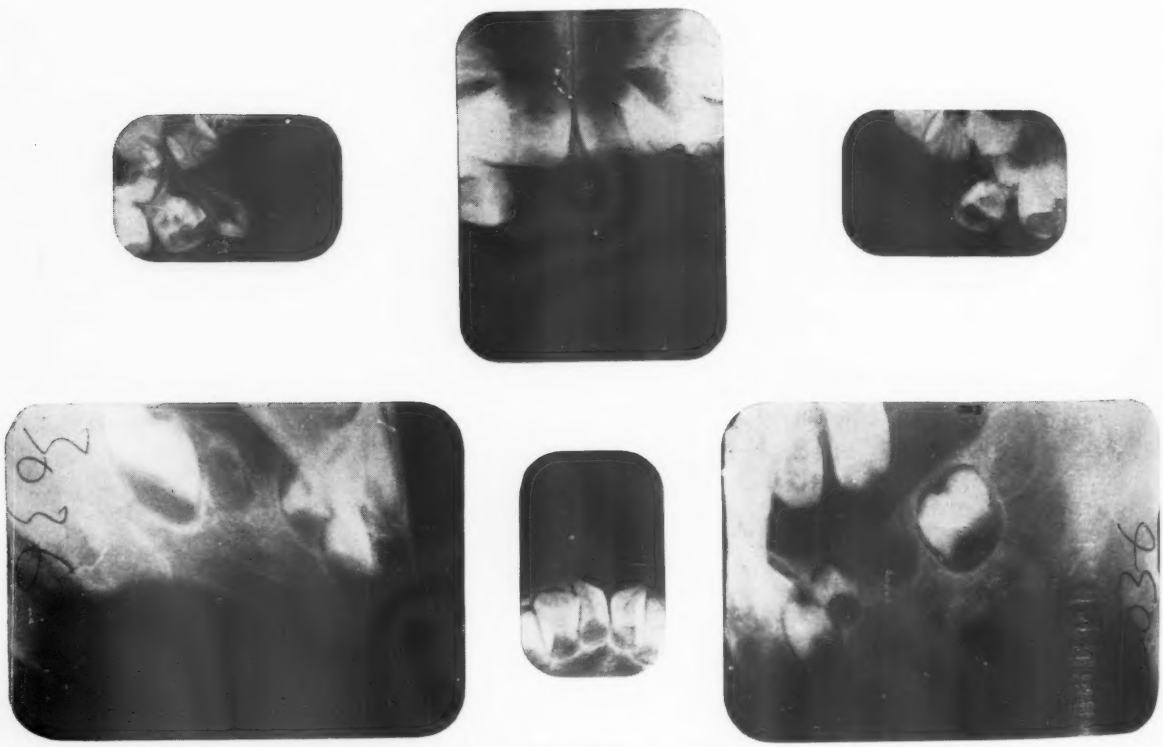

FIG. 4.—Radiographs taken at 3½ years of age showing the developing permanent teeth of this patient.

at the age of 3 years he had only seven deciduous teeth in his mouth (Fig. 2).

There was no family history of bone deformity or of abnormality of teeth.

On examination he was a healthy-looking boy. Apart from his mouth and knees there were no abnormal physical signs. The hair, finger nails and skin were normal. When the knees were placed together in the supine position, the internal malleoli were 1½ in. apart.

Examination of the mouth showed a narrow upper dental arch with a high vaulted palate (Fig. 1). The gums were normal. The remaining teeth were normal in appearance and free from caries.

Upon examining a lower deciduous molar immediately after exfoliation the macroscopic appearance (Fig. 3) was similar to that of a deciduous molar normally shed at 10 years of age. Histological examination, however, of another of the lower second deciduous molars showed incomplete formation (corresponding to an age of about 1 year), with slight evidence of resorption. Radiological examination (Fig. 4) showed that the permanent teeth were present.

Other investigations showed that the urine was normal chemically and microscopically.

The Wassermann reaction was negative. The blood group was O Rh (D) positive.

The serum calcium, phosphorus and alkaline phosphatase levels were as follows:

Age	2 yr. 5 mth.	2 yr. 11 mth.	3 yr.
Serum calcium (mg./100 ml.)	11·5	11·2	10·8
Serum phosphorus (mg./100 ml.)	5·2	5·7	4·3
Serum alkaline phosphatase (Jenner-Kay units)	5·5	4	5

The serum albumin was 3·6 g. per 100 ml. and serum globulin 2·5 g. per 100 ml.

X-ray studies of the skeleton at the age of 4 years showed bowing of the tibia on both sides (Fig. 5) with a bone sclerosis occupying a triangular area in the upper end of the diaphyses mainly on the fibular side. The upper metaphysis of the tibia was tilted. Similar changes, though less marked, were present in other long bones. There was general osteoporosis of the pelvis.

FIG. 5.—*X*-ray photograph of tibia, showing bowing, tilting of the upper metaphysis, and a triangular area of sclerosis at the upper end of the diaphysis, mainly on the fibular side.

Discussion

The *x*-ray photographs of the tibia reproduced in the paper by Sobel *et al.* (1953) are indistinguishable from the *x*-ray picture in our patient, but they correspond exactly with those reproduced in a paper by Holt, Latourette and Watson (1954) concerning bowing of the legs in normal children, and regarded by them as normal. These authors regard the excessive medial calcification in the upper end of the tibia as secondary to the bowing. In their cases the bowing righted itself, so that the *x*-ray appearances were 'normal' by the age of 4. (The *x*-ray photographs of our case were taken at the age of 4.) It is not certain, therefore, whether our case should be regarded as having an osteodystrophy or not. There certainly appeared to be some degree of osteoporosis in the skeleton, but osteoporosis is difficult to assess.

The serum alkaline phosphatase level was consistently low in our case, but not as low as that described by other authors to whom reference has been made. Nevertheless, the similarity of our case

to that of Sobel *et al.* (1953) is so striking that it seems likely that the condition was the same.

It may be that the incomplete formation and premature absorption of the roots of the teeth was in some way associated with abnormal phosphatase activity. We have no other theory to offer.

Summary

We have described a boy aged 4 years who exhibited premature shedding of deciduous teeth. At 3 years of age he had only seven deciduous teeth remaining. It was shown that there had been incomplete formation and some premature absorption of the roots.

There was a genu valgum and doubtful radiological evidence of an osteodystrophy. The only abnormal biochemical finding was a low serum alkaline phosphatase level.

We wish to thank Dr. J. H. D. Millar of Scunthorpe for referring the patient to us; Dr. T. Lodge for the *x*-ray reports; Miss E. Finch, M.Sc., for the biochemical investigations; and the Photographic Department of the United Sheffield Hospitals for the photographs.

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EPILEPSY DUE TO BIRTH INJURY IN ONE OF IDENTICAL TWINS

BY

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One of the most cogent arguments used in favour of an inherited constitutional factor in the causation of idiopathic epilepsy is the finding that, if one of a pair of identical twins has fits, it is usual for the other to have frank epilepsy or at least an abnormal electroencephalogram (Lennox, 1947; Little and Weaver, 1950). Cerebral disease or injury, including birth trauma, may lead to epilepsy either by damaging a hitherto normal brain or, perhaps by a less severe lesion, by reducing the convulsive threshold in a predisposed individual. According to Nielsen and Courville (1951) the latter situation is much the commoner, and in Lennox's series of identical twin pairs in which one twin suffered from epilepsy following brain injury no less than half the non-epileptic co-twins had abnormal electroencephalograms. None of these studies was concerned with the pathology of the underlying birth trauma and we have thought it of interest to record the neuropathological findings in the following case of a child, the second of identical twins, who had suffered from what seemed to be a moderate degree of birth injury which had resulted in mental retardation and epilepsy. The child died after being in status epilepticus and only microscopical changes were found in the brain. The surviving twin is normal both clinically and electroencephalographically. It is noteworthy that such a gross degree of functional defect could be brought about in a child without genetic predisposition by a birth injury that failed to produce any gross distortion of brain structure.

Case Report

Mrs. P., a primigravida aged 24, had an uneventful pregnancy (apart from the recognition of twins in January) till May, 1950, when she developed pre-eclamptic toxaemia. As she was only a week from her expected date of delivery, medical induction was undertaken and labour began. After eight hours it was deemed advisable to rupture the membranes and meconium-stained liquor was obtained. The first twin was born by the vertex rather less than two hours later; he was in good condition and cried well. Ten minutes later the membranes of the second twin were ruptured and again the liquor was stained with meconium: this baby was delivered by breech extraction with some difficulty and was slow to cry. Soon after the second twin a single, uniovular placenta was expelled intact. The first twin weighed 4 lb. 14 oz. at birth, and the second 5 lb. 3 oz. Both babies were in an oxygen tent for the greater part of the first two days, this being the routine for premature babies at that time.

Apart from physiological jaundice, the smaller twin (Julian) made normal progress in the neonatal period and has continued to make normal progress ever since. The second and larger twin (Roger) after 48 hours was noted to have periods of very poor colour and was jaundiced, the hands and face twitched and he breathed irregularly. The rectal temperature was 103·6° F. and penicillin was therefore prescribed. As the fontanelle was not tense and there was no neck stiffness, lumbar puncture was not performed, but chloral, grain ½, was given every half hour till twitching ceased. Vitamin K and subcutaneous glucose were administered in addition. That evening the temperature (rectal) reached 105·6° F.

During the next three days, the temperature fell, colour improved and there was no recurrence of twitching; feeding was satisfactorily established and intramuscular penicillin was stopped, though oral dosage was continued for another six days. Oxygen was intermittently administered for the first week of life.

Both twins had regained their birth weight by the fourteenth day, when they were discharged from the maternity hospital. Both were artificially fed. Right from this early date Roger was difficult with bottles and made slower progress than the smaller twin. Nevertheless, Roger was attempting to sit up and seemed to be able to recognize his parents at the age of 16 months. He then developed a cough with a tendency to vomit and had a fit in which he became blue, limp and unconscious. He was rushed to hospital where he was found to be barely febrile (100·2° F. rectally), although he was still twitching. The convulsion was easily controlled with intramuscular paraldehyde, but twitching recurred briefly later the same day. The cerebrospinal fluid was normal. No focal neurological signs were found and no

diagnosable infection developed. The child's mental retardation was all too obvious and he was discharged after five days.

There was some regression after this illness: he ceased attempts to sit and seemed less sure in his recognition of his parents. Progress was slowly resumed, however, and he learned to make some attempts at speech and to walk around the furniture. From the date of this illness he was constantly under hospital supervision and received anticonvulsant therapy. He had to be readmitted, however, on a number of occasions because of further convulsions.

In November, 1951 (aged 18 months), there was a suggestion of left-sided hypertonus, and both plantar responses were extensor. The cerebrospinal fluid was again normal.

In October, 1952, the left side seemed hypotonic after the fit, but all reflexes were symmetrically diminished.

In March, 1953, the convulsion was mainly right-sided, but on recovery no neurological abnormality was found. Plantar responses were flexor. In July, 1953 (aged 3 years 2 months), bilateral convulsive movements started at 7 a.m. and intermittent twitching occurred throughout the day in spite of therapy. He vomited some altered blood and his temperature rose inexorably. After two days he developed pulmonary oedema and died.

No electroencephalogram was ever attempted on Roger. He was too retarded to be likely to cooperate and the fact of epilepsy was hardly in doubt. There was, furthermore, no focal sign to suggest a lesion which might be surgically treated. An E.E.G. was undertaken on Julian, however, at the age of 4 and was reported as giving a tracing within normal limits for the age.

Evidence of Identical Twinning

Both boys were examined closely from this point of view in February, 1952 (aged 21 months), and were found to be 'identical' in general body configuration, in the colouring of hair and eyes, in iris pattern, in ear shape and in dental structure. The palmar creases were very closely similar and the finger print patterns were very similar in all four hands. Blood groups were investigated by Dr. R. A. Zeitlin, to whom we are grateful for the following results:

Father: A_1 R_1r(CDe/cde) M_sN_s K pos. Le^a neg. Le^b pos. Lu neg. P pos.
Mother: A_2 R_1R_1(CDe/CDe) M_sN_s K neg. Le^a neg. Le^b pos. Lu neg. P pos.
Roger, Julian: A_1 R_1R_1(CDe/CDe) M_sN_s K neg. Le^a neg. Le^b pos. Lu neg. P pos.

The finding of the intact uniovular placenta is also most important. It is, therefore, overwhelmingly probable that these boys were uniovular twins and were genetically identical.

Necropsy Report of Roger

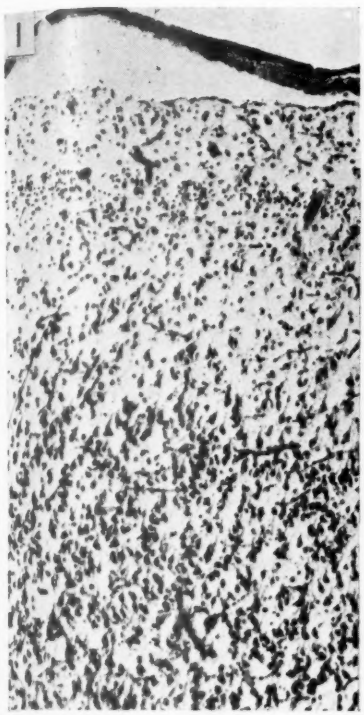
There was some excess of glairy exudate in the main air passages but no pneumonia and no cause was found to explain the fever. The brain looked entirely normal.

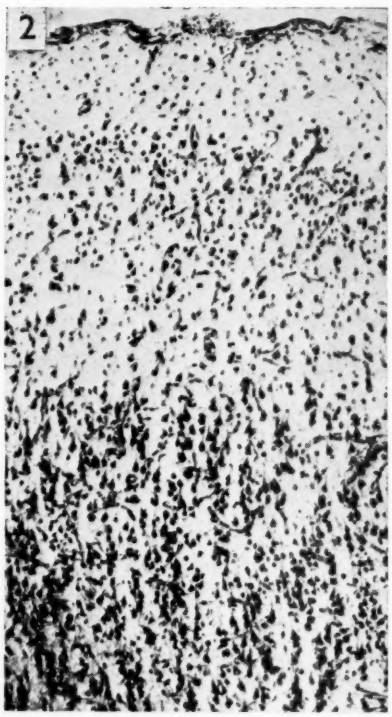
Brain. The brain weighed 983 g., of which the cerebellum and brain-stem accounted for 127 g. The vertex had become flattened during the process of fixation, but it was evident that the gyral pattern was normal and there were no signs of convolutional atrophy or localized softening. The corpus callosum, however, was unduly thin.

Blocks of tissue were taken from representative parts of the cerebral cortex, basal ganglia, cerebellum and brain-stem. Celloidin and frozen sections were prepared and stained for nerve cells, myelin, fibrous neuroglia and lipoid.

CEREBRAL CORTEX. Many parts of the cortex showed extensive areas in the third layer from which the great majority of the nerve cells had disappeared. In the temporal and occipital lobes the second layer was also frequently affected so that the larger pyramidal cells of the third layer often appeared to be the most superficial portion of the remaining cortex (Fig. 1). A similar type of incomplete laminar atrophy, though less widespread, was present in the region of the frontal poles (Fig. 2) and in the right insula. There was frequently a tendency for the depths of the gyral walls to be more affected than the crowns of the convolutions and in both visuosensory areas (O.C.) only the walls of the calcarine fissures were involved. On the right side the pyramidal cell layer of the uncus (Fig. 3) and of Ammon's horn in its Sommer sector were partially atrophied, the amygdaloid nucleus being unaffected. The hippocampal gyrus was intact. In all these areas of atrophy there was an overgrowth of the astroglia, but the overlying molecular layer did not show a severe marginal gliosis of the Chaslin type. The cortex was generally congested and the smaller blood vessels were unduly numerous in the areas of devastation. In some of these damaged gyri the medullary cores showed a mild diffuse loss of myelinated fibres, though elsewhere the staining of the central white matter appeared adequate for a child of this age. There was, nevertheless, a well-marked generalized fibrillary gliosis of the white matter, the density of which was unrelated to the degree of myelination. For example, in the left precentral gyrus where the myelination of both grey and white matter was particularly good and where there was no apparent diminution in the number of nerve cells, the gliosis of the central core was especially dense (Figs. 4 and 5). Small groups of fat-granule cells were occasionally seen around vessels in the cerebral white matter, but otherwise there was no indication of microglial activity. In addition to these longstanding lesions the cortex showed considerable recent damage attributable to the terminal status epilepticus. 'Areas of paling' of irregularly laminar distribution were present, mainly in the deeper part of the grey matter. In these areas the ground substance was rarefied or vacuolated, the nerve cells showing severe shrinkage and liquefaction with condensation of their basophil material into crenated formations. Spielmeyer's ischaemic nerve cell change was sometimes seen and some cells exhibited incrustation of the Golgi network.

BASAL GANGLIA. In the thalami the dorso-medial and the ventro-lateral nuclei showed extensive loss of





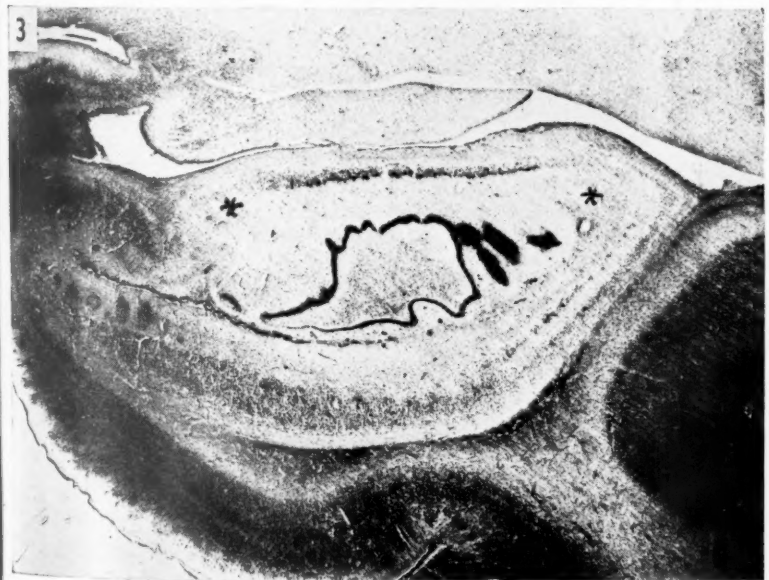


FIG. 1.—Right middle temporal gyrus showing diffuse loss of nerve cells in L2 and L3. Carbol azure ×60.

FIG. 2.—Left frontal polar cortex showing diffuse loss of nerve cells in L2 and L3. Carbol azure ×60.

FIG. 3.—Right uncus showing sectional losses in the pyramidal nerve cell layer (at *). The hippocampal gyrus is intact. Carbol azure ×6.

nerve cells with accompanying increase of glial nuclei and fibres. The right subthalamic nucleus appeared normal, as were each putamen and globus pallidus.

CEREBELLUM. Fibrillary gliosis was found in the white matter, but it was less conspicuous than in the cerebral hemispheres. Myelination was normal and the Purkinje cells present in normal numbers in the vermis and lateral lobes. Both dentate nuclei showed minor nerve cell losses.

BRAIN-STEM. The midbrain and pons appeared to be intact. In the medulla the inferior olives showed an abnormal gliosis in both the grey matter and the hila without associated cell loss. The pyramidal tracts were normal.

Discussion

Since it is unlikely that the patient's presumed neonatal infection or mild jaundice could have caused the extensive neuronal destruction found in his brain, it may be assumed with some confidence that an injury at birth had taken place, particularly in view of the breech delivery and the general retardation in the infant's development compared with the progress of the healthy identical twin. The absence of a genetically conditioned cerebral dysrhythmia, as proved by the surviving twin's normal electroencephalogram, indicated that the damage inflicted on the brain had been sufficient in its own right to cause the severe epilepsy from which this child suffered. The case was not, therefore, one in which birth injury had lowered the convulsive threshold of a predisposed individual.

The brain, however, showed none of the macroscopic features presented commonly by the late sequelae of birth trauma, there being no cystic softenings or sclerotic microgyria (Benda, 1945, 1952; Norman, 1953). The histological findings had some points of resemblance to the 'diffuse patchy cortical devastation' described by Benda in cases of birth injury and attributed by him to venous stasis. In this group, however, additional sub-cortical and striatal lesions

FIG. 4.—Left precentral gyrus showing normal myelination. Kultschitsky-Pal stain ×1·7.

FIG. 5.—As in Fig. 4, showing fibrillary gliosis in the white matter. Holzer stain ×1·7.

were usually present and the areas of cortical neuronal necrosis were more irregularly distributed than the essentially laminar lesions in our case. Diffuse atrophy of the third cortical layer is common to many anoxic and ischaemic conditions (Courville, 1953) and the segmental lesions of the pyramidal cell layer of the uncus and cornu Ammonis are also well known sequelae of anoxia. There was no sclerosis of the hippocampal gyrus itself in our case so that it is unlikely that the changes in the right temporal lobe were the result of herniation of the hippocampus into the tentorial incisura, a mechanism recently described in certain cases of birth injury by Earle, Baldwin and Penfield (1953). The simplest interpretation of the pathological findings in this brain would therefore be that they followed birth anoxia with its associated circulatory disturbances.

There remains, however, the problem of the possible relationship of the brain damage to the patient's epilepsy. Scholz (1951) has convincingly shown that widespread neuronal destruction of a selective character may follow the functional vascular disturbances which are associated with fits, especially when these occur in young individuals. The pattern of these lesions closely resembles that produced by cerebral anoxia and includes laminar cortical atrophy, sclerosis of Ammon's horn, gliosis of the white matter and areas of nerve cell loss in thalamus and dentate nucleus—all structures affected in this brain. Perhaps the involvement of the calcarine cortex in our case is a small pointer in favour of a primary birth injury, since this area is often spared in a remarkable way in epilepsy. However, it would also be true to say that birth anoxia often damages the corpus striatum, which was a centre unaffected in this case.

The evidence is therefore equivocal, and clear-cut distinctions between these two varieties of destructive process may be impossible on histological grounds alone. Apart from the changes produced by the terminal status epilepticus, there was no evidence of recent brain damage, such as neuronophagia or microglial activity, which might have suggested the effect of a recent seizure; nor did the clinical picture indicate a progressive cerebral atrophy. Nevertheless, it is undeniable that the first major attack at 16 months caused a setback in the child's developmental progress, so that he lost some of his hard-won abilities such as sitting and standing and found great difficulty in regaining them. It is, therefore, not improbable that some additional structural damage was inflicted at this time. Scholz's (1951) cases of post-epileptic neuronal necrosis were considered to be examples of idiopathic epilepsy and in several there was a family history of fits. The present case suggests that symptomatic epilepsy due to birth injury may have similarly dangerous potentialities.

Summary

The neuropathological findings have been described in a case of birth injury affecting one member of a pair of identical twins. The injured twin was mentally defective and epileptic, while the co-twin is healthy and has a normal electroencephalogram. The brain showed no naked-eye abnormality, but microscopically there was widespread longstanding neuronal atrophy involving mainly the outer cortical layers, the cornu Ammonis and thalami. It is considered that most of these lesions occurred at the time of birth, but that additional brain damage may have followed a severe fit in infancy.

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PULMONARY CYSTS FOLLOWING INGESTION OF HOUSEHOLD PARAFFIN

BY

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This is the rather unusual case of a small boy who developed an acute pneumonia with multiple cystic cavities in the lungs after drinking household paraffin or kerosene. There was complete resolution in a few weeks, and a striking absence of physical signs in the chest.

The boy, aged 2½ years, was brought to the North Cambridgeshire Hospital, Wisbech, on June 18, 1954. The mother gave the following history.

On the day before admission the child drank about three-quarters of a one-pound jam jar filled with 'Aladdin' pink paraffin. The child was given 1½ teaspoonfuls of 'syrup of figs' and a mineral drink, and remained quite well until the evening, when it was noticed that he looked pale and apathetic, his breath smelling strongly of paraffin. He did not vomit or cough that day. The following morning he looked ill, very pale, and he refused food, though not complaining of any pain or discomfort. The past history revealed that the boy was the sixth child of the family, weighing 7 lb. 5 oz. at birth. There were no complications of pregnancy, delivery or infancy. The family history did not reveal anything of interest.

On admission his temperature was 102° F., pulse 140, and respirations were 45. No abnormality was found in the respiratory system except that his respirations were grunting and the breath sounds harsh. The child was rather lethargic, pale, slightly cyanosed, and clearly distressed and dyspnoeic. He passed a large offensive motion which blistered his buttocks. Haemoglobin was 12·8 g., the white cell count 12,000 (55% polymorphs, 40% lymphocytes and 5% monocytes).

A radiograph taken on that day presented the appearance of bilateral pulmonary collapse affecting probably the right middle lobe, the lingula and both lower lobes (Fig. 1). The child was put in an oxygen tent and treated with 250,000 units of crystalline penicillin four-hourly. His temperature and respiration rate gradually settled down during the next three days, and he appeared to be making a satisfactory recovery. On June 23, the fifth day after admission, the temperature rose again to 103° F., the pulse to 140 and the respirations to 45. The child again looked acutely ill and distressed. Aureomycin was given, 100 mg., six-hourly.

After this his temperature gradually settled down, and within the next four or five days his general condition improved, although he appeared very ill for about two weeks. He remained in an oxygen tent all that time. His appetite gradually improved and he gained some weight. A radiograph taken 15 days after admission showed a cavity in the right lung, at the site of the lower zone collapse in the previous radiograph. It was round,

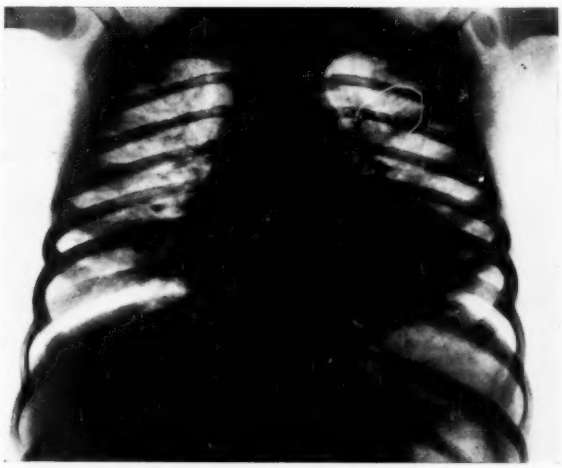
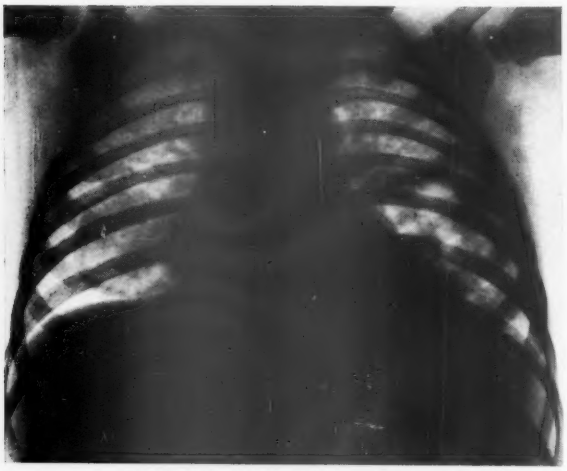


FIG. 1.—Radiograph taken on the day of admission, June 18, 1954.

4 cm. in diameter, the thickness of the wall being 4 mm. There was no fluid level.

In the left lung there was a system of cavities in the middle and lower zones, occupying the site of the former collapse, of similar appearance to that described above. Right and left lateral films confirmed multiple cavities in the right middle lobe and left lingula and lower lobes (Figs. 2 and 3).

A blood examination taken on the eighteenth day after admission showed a haemoglobin of 12·2 g. with 3,290,000 R.B.C.s, 5,000 W.B.C.s (polymorphs 26%, lymphocytes 68%, monocytes 6%). A radiograph on that day showed a fluid level in the right basal cavity which by a week later had shrunk to about 1 cm. in diameter. The fluid level remained. The cavity was



FIGS. 2 and 3.—Radiographs taken 15 days after admission on July 2, 1954, showing multiple cavities.

surrounded by atelectasis of the medial segment of the middle lobe.

In the left lung there was marked reduction in the size of the cavities, and no fluid levels.

The child remained apyrexial, and no abnormal physical signs were found except for a few rales at both bases. He was treated with daily postural drainage and percussion.

Subsequent radiographs showed a further reduction in the size of the cavity in the right lung, clearing in the lower zone of both lungs, and finally complete disappearance of the cystic spaces. He was transferred one month after admission to a convalescent home. On his return, three weeks later, radiographs showed further clearing and re-expansion of the collapsed part of the lower lobes. The child remained well, gaining weight, and a film taken two months after admission showed some right basal collapse but no cystic changes.

Discussion

The literature, especially from America, contains a number of references to kerosene poisoning and pneumonia.

Lesser, Weens and McKey (1943) found in their series of experiments using rabbits that pulmonary manifestations in these animals were more likely to be due to aspiration of the kerosene into the lungs than to absorption via the intestinal tract.

Experiments on dogs and rabbits by Richardson and Pratt-Thomas (1951) have indicated that, assuming conditions in these animals to be comparable to children weighing 50 lb., then, provided that aspiration does not occur, a volume in excess of a pint would have to be swallowed to prove fatal. The patient described here swallowed almost a jam jar full of kerosene, and would thus seem to have drunk a potentially lethal dose. On the other hand, however, if only slightly more than a teaspoonful were aspirated, severe pneumonia with an almost certain fatal outcome would result.

Theoretically one can suppose that paraffin can reach the lungs via the intestine. Frazer, Shulman and Stewart (1944) have shown that fine emulsions may be absorbed from the rat's intestine in particulate form, pass along the lacteals to the thoracic duct and then through the great veins into the right heart and lungs.

It might be argued that the cause of pulmonary complications following the drinking of kerosene is in fact aspiration, the child reacting to the unpleasant taste by choking and vomiting. While this is clearly possible, it is not in fact true that the taste of kerosene is at all unpleasant, as anyone who has tried it will agree.

In this case, however, as the large quantity of kerosene ingested could itself account for the severity of the subsequent pneumonia, and as this did not develop until 24 hours later, it does not seem necessary to invoke aspiration as one of the mechanisms of the disease.

Deichmann, Kitzmiller, Witherup and Johansmann (1944) described histological findings in kerosene pneumonia. These consist of oedema and vascular congestion with focal areas of acute interstitial inflammation and haemorrhages. The alveoli contain inflammatory exudates consisting of fluid fibrin and white blood cells and foreign body giant cells. In extreme cases the entire tracheobronchial tree is filled with this exudate and the mucosa of smaller radicles shows ulceration in places.

Radiological appearances vary from small patchy densities in the costophrenic angles to the large mottled densities of severe cases. The pulmonary

changes are seen more commonly bilaterally, and are usually more pronounced in the base of the right lung. The changes are more consistent with those of hyperaemia or oedema than of pneumonitis.

Changes in the lung were observed to occur rapidly after kerosene ingestion, and resolved usually after two weeks. In spite of the fact that kerosene in contact with the body tissues may result in fibrosis, complete resolution with no evidence of permanent tissue damage is usually found.

The remarkable feature in the case described is the formation of cysts in the lungs. It is considered that the *x*-ray appearances were caused by tension cyst formation rather than by destruction of lung tissue. This view was based on the rapidity with which recovery occurred and on the fact that no appreciable increase in the white blood cell count was found. There is no reference in the literature to tension cyst formation following kerosene pneumonia. Hodson and Neill (1948) described six cases in which air-containing spaces were found occurring in a variety of pulmonary lesions; staphylococcal pneumonia, lobar pneumonia, fluid-containing cysts (probably congenital), localized pneumonic consolidation and in one case consolidation and collapse without pyrexia. In the present case the radiological appearances may have been a direct result of paraffin ingestion, or to secondary infection such as the staphylococcal infection described by Hodson and Neill. The latter supposition may be supported by the rapidity with which the condition subsided with antibiotics.

Summary

A case is described of bilateral pulmonary tension cysts in a $2\frac{1}{2}$-year-old child after drinking kerosene.

My thanks to Dr. B. W. Powell for permission to publish this case and to him and Dr. Downes for their criticism and helpful suggestions.

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CONGENITAL THYROTOXICOSIS, HEPATOSPLENOMEGALY AND JAUNDICE IN TWO INFANTS OF EXOPHTHALMIC MOTHERS

BY

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This paper describes two infants with congenital enlargement of the thyroid and hepatosplenomegaly. One infant died at birth from obstetrical causes, the other lived for 33 days, during which time he was thyrotoxic and jaundiced. Though the first infant was not jaundiced, and, naturally, showed no signs of thyrotoxicosis, we consider that he showed all the other features of the syndrome.

Maternal History

Both infants were the offspring of mothers who had undergone thyroidectomy for Graves's disease, two years and four years respectively, before the birth of the affected infant. In both mothers the course of the thyrotoxicosis was unusual in that there was no weight loss during the course of the disease and the exophthalmos persisted unchanged after operation. We consider that both women had a supra-thyroid (pituitary) type of thyrotoxicosis, and that the anterior pituitary continued to be overactive after the operation. The mother of the first infant was treated pre-operatively with Lugol's iodine and phenobarbitone. The mother of the second infant received Lugol's iodine and thiouracil before her operation. Neither of these women was thyrotoxic during her pregnancy, though the exophthalmos was marked. Their ages were 21 and 25 respectively at the time of delivery. The mother of the first infant was thought, two months after delivery, to show some very minor signs of thyrotoxicosis. At that time her basal metabolic rate was +31%. There was a fine tremor and some tachycardia, but her exophthalmos was out of proportion to the toxic signs and she had lost no weight. The mother of the second infant was not thyrotoxic during or after her pregnancy, and gave birth to a normal living female infant 16 months later. There was no evidence of syphilis, toxoplasmosis or blood group incompatibility in either of the mothers or the infants. The 24-hour 17-ketosteroid excretion in the first mother was estimated two months after delivery, and was 8·65 mg. %.

Infants' History

The birth weight of the first infant was 3 lb. 15 oz. He was born by spontaneous vertex delivery, and his immediate post-natal condition was good. On the third day his weight had dropped to 3 lb. 5 oz. Throughout the first week he was abnormally active and restless, and appeared ravenously hungry. He became slightly dehydrated and moderately jaundiced at the end of the first week. At that time phenobarbitone, grains $\frac{3}{4}$ daily, only just controlled his hyperactivity, but did not prevent his taking 3 oz. of expressed breast milk every three hours. On the eleventh day (Fig. 1) he was very

FIG. 1.—The thyrotoxic infant on the eleventh day.

emaciated and his jaundice was more marked. The skin was moist, the urine dark, and the stools were pale. There was a suggestion of a stare and exophthalmos. The thyroid was visibly enlarged, the liver reached three fingerbreadths, and the spleen two fingerbreadths, below

the costal margins. There was a regular tachycardia of 170 per minute.

From the 11th to the 33rd day of life the infant continued to be overactive and very hungry, taking avidly from the breast. Continuous sedation was necessary. In spite of an unlimited supply of milk he did not regain his birth weight. The jaundice and exophthalmos fluctuated slightly, but did not disappear. The hepatosplenomegaly and the enlargement of the thyroid persisted unchanged. After the third week of life his pulse declined from 170 to 140, but did not drop below this figure. On the 33rd day of life his temperature, which had been normal throughout, rose to 105° F., and he was found to have a bronchopneumonia, to which he succumbed after 24 hours in spite of treatment.

Laboratory investigations gave the following results:

The direct Coombs test was negative, and the indirect van den Bergh gave 1·2 mg. at eight days, 4 mg. at 19 days.

Radiographs of the chest and a skeletal survey were normal.

A blood count at 11 days gave: 129% Hb, 9,000 W.B.C. (52 polymorphs, 1 eosinophil, 42 lymphocytes, 5 monocytes) at 19 days, 149% Hb, 1,500 W.B.C. (33 polymorphs, 3 eosinophils, 46 lymphocytes, 8 monocytes).

In the urine there was a trace of a reducing substance, but no bile salts, no urobilin and a trace of bile pigments, but no cytomegalic inclusion bodies.

There was no excess galactose in the serum. The blood sugar level was 57 mg. %, the blood cholesterol level 144 mg. %. The prothrombin time (Quick's method) was 15 seconds.

The C.S.F. contained 25 mg. protein, 46 mg. sugar, 1 lymphocyte, 7 red blood cells.

In the stools there was trypsin but no urobilin.

The second infant was born after a labour lasting 39 hours and 25 minutes. His birth weight was 4 lb. 7 oz. He was shocked and asphyxiated, and though the heart continued to beat for 15 minutes, he died without having breathed, in spite of intubation and phrenic nerve stimulation. He was not icteric.

Morbid Anatomy

Case 1. Necropsy was performed 48 hours after death.

The body is that of a male infant weighing 1·6 kg. There is moderate jaundice of the skin and sclerotics. The body appears wasted and dehydrated and the skin wrinkled, and there is no buccal pad of fat. The neck appears fuller than normal.

The thyroid (weight 4·6 g.) is uniformly enlarged (Fig. 2); the lateral lobes measure 3 cm. in length, 1·4 cm. in width at the lower poles and 1·1 cm. anteroposteriorly. The thyroid is pale brown and normal in consistency and no colloid is visible on the cut surface. Microscopically there is a definite slight increase in fibrous tissue with thickening of the connective tissue septa. This divides the thyroid tissue into a number of small lobules each consisting of groups of small acini which are packed together, the walls lined by hyperplastic epithelium. The acini contain no colloid and consequently appear as small nodular aggregates of cells. The epithelial cells have relatively scanty cytoplasm and the nuclei are rather large and dark staining. Many cells are binucleated. There are no lymphorrhages. There is no congestion of the gland (Fig. 3).

The thymus (12 g.) appears normal macroscopically and microscopically.

FIG. 2.—The enlarged thyroid of the first infant.

The liver (112 g.) is enlarged uniformly and dark brownish green. Its shape is normal and on section the parenchyma feels firmer and more resistant than normal. There is no gross evidence of cirrhosis. Microscopically there is an early cirrhosis; in the portal areas there is fibrosis and proliferation of bile ducts. From these areas a fine fibrosis radiates out between the columns of liver cells, and an early multilobular cirrhosis is developing. The fibrosis also extends between the liver cells, breaking them up into short columns (Fig. 4). There are a few foci of haemopoiesis in the sinusoids and portal areas. The liver cells are rather small and contain brown pigment granules, apparently bile, and the bile canaliculi contain plugs of dark green bile. Occasional large multinucleated hepatic cells are seen. The Kupfer cells are swollen and contain pigment granules. A few hepatic cells contain a fine powdering of iron pigment.

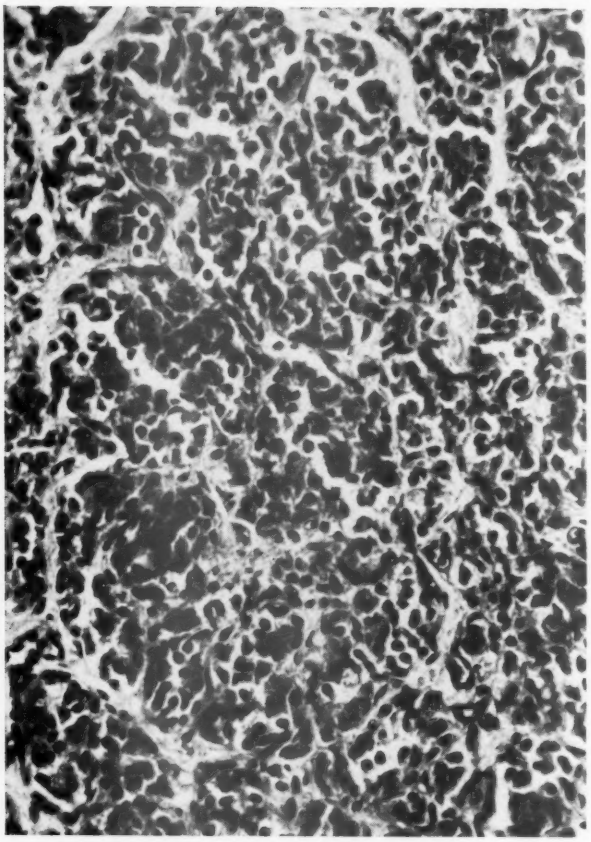

FIG. 3.—Thyroid showing marked cellularity. Acini not distinguishable, no colloid present. (Haematoxylin and eosin × 270.)

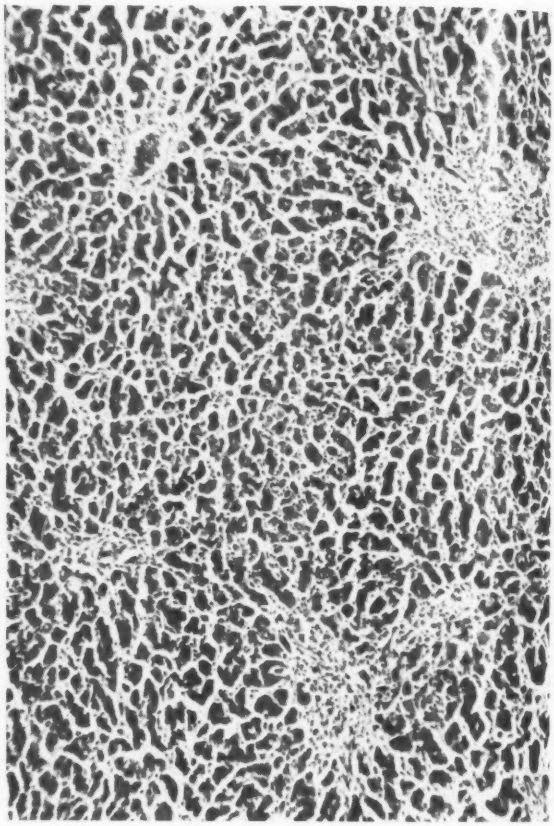

FIG. 4.—Liver showing early cirrhosis with fibrosis starting around portal areas and radiating out therefrom. (Haematoxylin and eosin × 65.)

The gall bladder and extrahepatic bile ducts are patent.

The spleen (weight 9 g.) is enlarged, and on section shows a moderate degree of congestion.

The lungs show a bronchopneumonia.

The retrobulbar tissues show no abnormality.

All other tissues and viscera appear macroscopically and microscopically normal.

Case 2. The body is that of a premature male infant weighing 2·00 kg. There are numerous petechiae in the skin of the trunk and limbs, but no evidence of injury. The neck appears abnormally full, the veins of the neck are congested and the face cyanosed. There is no jaundice or generalized oedema, but the conjunctivae are oedematous and show a few minute haemorrhages.

The thyroid (8 g.) has a volume of 9 ml. Both lateral lobes and the isthmus are symmetrically and uniformly enlarged. The lateral lobes are 3 cm. long, 2 cm. wide at the lower poles and 1·5 cm. anteroposteriorly. On gross section the parenchyma is dark red, of a homogeneous appearance and shows no colloid on the cut surface. The enlarged thyroid closely embraces the trachea but does not appear to have caused any mechanical obstruction. Microscopically the thyroid tissue is considerably autolysed and the veins and capillaries are congested. The acini are small and closely packed, the epithelial cells are of cuboidal type, in some places several cells thick on the basement membrane. Most of the small acini show small clumps of desquamated epithelial cells in the lumina. There are numerous irregularly shaped haematoxylin staining masses composed of three or more fused nuclei. There is no colloid or lymphoid tissue.

The thymus (23 g.) is enlarged, an appearance which, on microscopic examination, is seen to be due to congestion only.

The liver (150 g.) is uniformly enlarged but of normal shape. The parenchyma on gross section is normal in colour but congested. Microscopically the hepatic veins and sinusoids are congested. There is a considerable amount of haemopoietic tissue in the sinusoids and portal areas. The parenchyma cells are somewhat autolysed and many show intracellular masses of bile pigment. There are small collections of bile pigment in the canaliculi. The Kupfer cells are swollen and contain bile pigment. No iron is present. There is early proliferation of bile ducts in some of the portal areas and a very early proliferation of reticulum fibres round the

portal areas and between the liver cells, indicating an early diffuse fibrosis.

The gall bladder contains bile and the bile ducts are patent.

The spleen (24 g.) is uniformly enlarged. Microscopically this enlargement is due to intense congestion.

The heart shows a few subepicardial petechiae.

The lungs show a few similar petechiae beneath the pleura and are not expanded.

Examination of all other viscera shows no significant change macroscopically or microscopically.

The thyroids of both these children show a picture of hyperplasia of the epithelium. This is particularly marked in Case 1, with no colloid formation.

The appearances of the liver in Case 1 are those of an early diffuse hepatic fibrosis. The process is beginning in the portal areas and extending from thence towards the centres of the lobules, and is also extending between liver cells. The bile plugs in the canaliculi suggest an obstructive element that is probably secondary to the fibrosis, and there is no obstruction of the extrahepatic bile channels. The liver in Case 2 shows a very early stage of this process of fibrosis.

The enlargement of the spleen is congestive in nature and probably indicative of a slight portal hypertension in Case 1, secondary to the hepatic fibrosis. In Case 2 it is probably a further expression of the generalized congestion of all viscera which is much more marked in Case 2 than Case 1.

Discussion

Jirsová and Brychnáč (1953) described an infant who appeared in almost all respects identical with our two cases. His mother had persistent exophthalmos after a partial thyroidectomy. Two years after operation she gave birth to a child whose birth weight was 2,106 g. and dropped to 1,930 g. after two days. The baby was overactive and ravenous, and his muscle tone was increased. He had exophthalmos, a stare and a persistent tachycardia of 180. The sclerae were icteric and the stools were clay coloured. The thyroid was visibly enlarged, and the liver and spleen were enlarged 2 cm. and 3 cm. respectively below the costal margins. He made a spontaneous recovery, and at the age of 3 months his exophthalmos was barely noticeable, his pulse was 120, his weight was 4,300 g., and the goitre, jaundice and hepatosplenomegaly had disappeared.

We have been unable to find any other cases of this kind in the literature. It would appear that our two infants, and the infant described by Jirsová, differ materially from the three cases of congenital thyrotoxicosis which have been recorded. White's case (1912) was the offspring of a mother who developed thyrotoxicosis—not treated by operation—when she was five months pregnant. The child weighed 4 lb. 6 oz. at birth, had a tachycardia of 200, exophthalmos, tremor of the hands and a uniform enlargement of the thyroid. He died 36 hours after birth, probably from a cerebral birth injury. Margetts' infant (1950) was reported by his mother to have been lethargic and difficult over his feeds at first. His birth weight was 5 lb. 13 oz. When first seen at the age of 4 weeks he was thin and restless, blinked infrequently, and the palpebral fissures were widened. He had a tachycardia of 160 to 200. However, the thyroid was not palpable. At the age of 3 months the exophthalmos and hyperkinesis had diminished and his pulse was 135 to 160. His mother had been thyrotoxic for one year before delivery. Her disease had worsened during pregnancy and had been treated with phenobarbitone and digitalis. Fischer (1951) reported an infant whose mother developed thyrotoxicosis during the last trimester of her pregnancy and had been treated with propylthiouracil and sedatives. The baby weighed 7 lb. at birth and was restless and difficult to feed during the first week of life. He was pyrexial, dehydrated and slightly cyanosed, and had a tachycardia. Fullness of the neck, hoarseness, tremor, moist skin and exophthalmos became apparent during the second week. The cyanosis, pyrexia and dehydration did not disappear until the child was 4 weeks old, in spite of oxygen, penicillin and subcutaneous fluid therapy. Lugol's iodine, given at 3 weeks, had no effect on the signs of thyrotoxicosis. These slowly subsided between the fourth and tenth weeks, at which time the neck was still full and slight exophthalmos was still noticeable.

Neither jaundice nor hepatosplenomegaly was a feature of any of these cases of congenital thyrotoxicosis. The thyrotoxicosis was evidently the result of an excess of maternal thyrotropic hormone reaching the foetus via the placenta. This would explain the transient nature of the disease in the infants who survived. No doubt the thyrotoxicosis in our and Jirsová's cases was due to a similar mechanism.

It is interesting that all the reported cases of congenital thyrotoxicosis have occurred in male infants. The usual sex incidence of the disease in children is given by Kennedy (1950) as five females to one male. Possibly the female foetus is better equipped to neutralize in some way her mother's excess thyroid-stimulating hormone. It will be noted that the mother of our second infant subsequently gave birth to a normal female child though her pituitary was then still producing excessive amounts of thyroid-stimulating hormone.

We can only speculate as to the cause of the jaundice and the enlargement of the liver and spleen in which our and Jirsová's cases differ from those of

White, Margetts and Fischer. The mothers of the former infants had all undergone thyroidectomy at varying periods before delivery, and had continued to show signs of thyrotoxic hormone excess during and after the birth of their infants. We feel that this continued excess of thyrotropic hormone may be responsible for the hepatosplenomegaly and jaundice which complicated the congenital thyrotoxicosis in Jirsová's and our cases. On the basis of the six infants described, it would appear that women who continue to produce an excess of thyroid-stimulating hormone after their thyroxin output has been reduced to normal by thyroidectomy can give birth to infants with congenital thyrotoxicosis, hepatosplenomegaly and jaundice. The offspring of women not operated on for their thyrotoxicosis may show an uncomplicated congenital thyrotoxicosis. No help can be gained in this problem from animal experiments, as nothing appears to be known of the effect on the foetus and neonate of maternal, pituitary, thyrotropic hormone excess.

The hepatosplenomegaly and jaundice may have been due to thyrotoxic liver damage, an established complication of thyrotoxicosis in adults. However, it seems improbable that such damage could have occurred in such a short time, or that it could have occurred *in utero*, as one would have to postulate in our second case.

Lastly, a neonatal hepatitis complicating the congenital thyrotoxicosis must be considered as a cause of the jaundice and hepatosplenomegaly. Neither the clinical picture nor the histological findings in the liver support such a diagnosis, and neither of the infants' mothers had suffered from infectious hepatitis.

Summary

A clinical and pathological account is given of two infants with a syndrome of congenital thyrotoxicosis, jaundice and splenomegaly. Their mothers had been operated on for thyrotoxicosis, and had continued to show signs of thyrotropic hormone excess after operation, during pregnancy and after delivery. It is suggested that this excess of thyrotropic hormone may account for the disease picture found in the infants.

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SUPPURATIVE PERICARDITIS DUE TO A PENICILLIN- AND STREPTOMYCIN-RESISTANT STAPHYLOCOCCUS

BY

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(RECEIVED FOR PUBLICATION APRIL 15, 1955)

In spite of modern antibiotic therapy, suppurative pericarditis remains a serious condition and the mortality rate is still believed to be in the region of 50% (d'Abreu, 1953). Aird (1949) states that the mortality by aspiration alone is 100%, by operation alone 50%, but that the mortality from a combination of aspiration and penicillin replacement should be low providing the organism is sensitive to antibiotics.

Treatment by aspiration and antibiotic replacement is likely to be ineffective if there is loculation within the pericardial sac when cardiac compression might occur, and when the antibiotic cannot penetrate into the pockets of loculated pus.

The following case is reported in view of the initial difficulty in diagnosis and the inadequate response to aspiration and replacement therapy, as well as the resistance of the infecting organism to the antibiotics that are usually considered most suitable for intrapericardial instillation. The child's father is a doctor, and this may account for the unusual resistance of the organism, which one could expect to find in a 'hospital infection' rather than in one acquired in the home.

Case Report

C.W., a girl aged 21 months, was admitted to the Children's Hospital, Birmingham, on June 30, 1954, because of a pyrexia of uncertain origin. She had been ill for five days and was irritable and refusing food; the temperature had been raised from the onset and had reached 102° F. before admission. She had been given oral penicillin by her own practitioner.

On examination she was seen to be a well nourished, irritable, ill-looking child. A short expiratory grunt was heard with each respiration, but there was no cyanosis. Temperature 102° F., pulse 120, respirations 28. No abnormal physical signs could be detected.

A chest radiograph showed no lesion. A leucocytosis was present (see Table). Routine agglutination tests were negative.

The child was treated empirically by a systemic course of chloramphenicol which was begun on July 1. The temperature fell to normal on the sixth day of antibiotic treatment which was continued for a further two days, that is up to July 8.

On July 5 a pericardial friction rub was present, and a chest radiograph at this time showed a large heart shadow and on screening there was feeble pulsation suggestive of a pericardial effusion.

As the child was afebrile at this stage the possibility of a serous effusion or a Fiedler's myocarditis was considered. Pericardial aspiration was not performed until the temperature rose again a week later.

Five days after the chloramphenicol had been discontinued, on July 13, the temperature again rose to 100° F. The leucocytosis was still present (see Table).

On July 14 the child was still pyrexial and pericardial aspiration was performed via the xiphicostal angle;

TABLE
LEUCOCYTE COUNT

1954	Total W.B.C.	Total Granulocytes	Polymorphonuclears		Metamyelocytes	Hb (g. %)
			Segmented	Unsegmented		
June 30	19,000	11,980	9,690	1,330	760	11·3
July 3	17,700	11,859	11,328	354	177	10·5
July 12	20,000	12,600	12,000	400	200	9·2
July 19	25,000	16,750	16,000	750	0	
Blood transfusion was given on July 21						
July 26	19,800	9,306	8,514	792	0	13·7
Aug. 11	16,000	8,620	28,300	320	0	
Aug. 19	18,500	13,470	11,100	370	0	13·4
Aug. 31	13,000	6,110	6,110	260	0	11·9

50 ml. of turbid fluid were withdrawn and 1 mega unit of soluble penicillin was introduced into the pericardial sac. A course of systemic penicillin was begun before completion of the bacteriological sensitivity tests as there was no reason to consider that the organism would be penicillin insensitive.

Cultures of the fluid produced on July 15 a pure growth of coagulase-positive staphylococci. The actual pus was also inoculated on to the routine sensitivity plates and this showed that the staphylococci were insensitive to penicillin and streptomycin, partially sensitive to chlortetracycline and sensitive to chloramphenicol, oxytetracycline, neomycin and erythromycin. In view of the recent administration of chloramphenicol it was felt advisable that systemic therapy should be provided by erythromycin. No preparations of oxytetracycline, neomycin and erythromycin at this time were suitable for local intrapericardial instillation. However, a pharmaceutical firm informed us that they had available a 15% micronized suspension of chloramphenicol (Sorsby, Unger and Crick, 1953) which it would be safe to instil into the pericardial sac. A supply was dispatched which allowed us to employ locally an effective antibiotic within 24 hours of the initial paracentesis.

Pericardial aspiration produced 70 ml. bloodstained turbid fluid, and 8 ml. of the 15% chloramphenicol suspension (1·2 g. chloramphenicol) were introduced.

Pericardial aspiration on July 16 produced 20 ml. of fluid, and 8 ml. of chloramphenicol suspension were introduced. The fluid still grew a few staphylococci, and the temperature was 100° F. On examination, there was considerable 'muffling' of the heart sounds, the neck veins were beginning to distend and the liver was enlarged to three fingers below the costal margin. Loculation within the pericardial sac with cardiac compression appeared probable and it was decided to institute open drainage. A chest radiograph confirmed the presence of a large cardiac outline, and a moderate left pleural effusion was also present.

Under general anaesthesia on July 16 a pericardiostomy was performed after resection of 2 in. (5 cm.) of the seventh left costal cartilage (Donaldson's approach, 1943). Owing to the presence of the pleural effusion, the left pleura was inadvertently opened. Intrapericardial loculations were broken down with the finger and pus and fibrinous clots evacuated, the pus being present under tension. Three fine rubber catheters were inserted, one to the right of the pericardial sac, one to the left and one in the oblique sinus. The parietal pericardium was sutured to the perichondral bed, and the superficial wound lightly packed with tulle gras. The left pleural cavity was drained by an intercostal tube attached to an underwater seal.

Chloramphenicol suspension was instilled daily (2 ml. into each catheter) for six days at the end of which time the catheters were removed: cultures of the pericardial sac were then sterile.

A chest radiograph on July 25 showed that the heart shadow was smaller.

By July 26 the child's temperature was 101° F. and respirations 40. There were signs of a fresh left pleural effusion which was confirmed by chest radiographs.

On July 27 pleural aspiration produced 250 ml. of yellow, turbid fluid, which proved sterile on culture, but in view of the possibility of pleural contamination at the operation, 4 ml. of the chloramphenicol suspension were introduced to the pleural cavity. Aspiration of the pleural cavity and instillation of the chloramphenicol were repeated for the next five days. All cultures of the pleural fluid were sterile.

On August 4 a chest radiograph showed the heart shadow to be slightly smaller; a small area of opacity (? consolidation) in the region of the apical segment of the left lower lobe was seen.

In view of this segmental opacity and the possibility of a metastatic staphylococcal lung abscess, a further course of erythromycin was begun and continued for three weeks.

The child's condition improved steadily and she was eventually discharged on September 1, 1954. She has been reviewed as an out-patient at intervals, and has remained well. The cardiac shadow remains moderately enlarged but the left lung opacity has cleared. There are no signs of chronic cardiac compression. The last radiograph taken on February 15, 1955, showed no change with moderate enlargement of the cardiac shadow.

We are indebted to Mr. A. L. d'Abreu for his advice on the treatment of this child, to Dr. Roy Astley for the radiological examinations, and to the ward sister and nurses for their devoted attention. We are especially grateful to Messrs. Parke, Davis & Co. for their very generous and extremely prompt assistance in making available to us supplies of the chloramphenicol suspension.

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ACUTE BENIGN PERICARDITIS IN INFANCY

BY

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Acute benign pericarditis is becoming more frequently recognized. Carmichael, Sprague, Wyman and Bland (1951) describe a series of 50 cases, and, in a review of the literature, suggest that the syndrome is becoming more common, especially in young adults. Friedman, Ash, Harris and Lee (1952) record the syndrome in infants of 5 months and 3 months of age respectively. A third possible example of the condition is described by Krost (1944), although this infant of 8 months was considered to have rheumatism, a non-specific aetiology seems more probable. Heindl (1948) describes a further case in a 5-month-old infant. The rarity of the syndrome in infancy has prompted us to describe a further case.

Case Report

A 7-week-old baby girl was admitted to hospital in November, 1954, with dyspnoea and vomiting. The birth weight was 5 lb. 5 oz. The child had been well up to eight days previously when she developed a cough and had difficulty in swallowing. Another child in the family had had an upper respiratory infection shortly before.

Physical examination showed a small infant of 8 lb. 9 oz. weight with considerable dyspnoea and subcostal recession. Temperature was 99° F., respirations 100 per minute, pulse 160 per minute. The throat was reddened and oedematous. There appeared to be little chest movement, and practically the whole of the chest was dull to percussion. The heart sounds could be heard but no bruit. A radiograph (Fig. 1) showed an enormously enlarged heart almost filling the whole of the thorax.

In spite of intensive chemotherapy with oxygen, the infant's condition deteriorated. The dyspnoea became more marked and the child became cyanosed. A paracentesis was performed and 25 ml. of clear, amber-coloured fluid were removed from the pericardium. The infant's condition improved, the cyanosis and dyspnoea becoming less pronounced. A gradual deterioration took place in the next few days, the cyanosis again becoming marked. A further paracentesis was performed. It was decided to remove as much fluid as possible and 150 ml. were aspirated very slowly. A dramatic improvement took place. The cyanosis and dyspnoea disappeared and full feeding was resumed. This procedure was repeated when the clinical condition warranted it. A total of 402 ml. of fluid was removed on eight occasions at about seven-day intervals. The last paracentesis was performed three months ago, since when the cardiac outline has remained within normal limits (Fig. 2). The child is now 7 months old, weighs 13 lb. 5 oz., and appears a normal thriving infant.

Investigations. A blood count showed a haemoglobin of 14·5 g. per 100 ml.; red blood cells 4·5 millions per c.mm.; white blood cells 23,000 per c.mm. with a differential count of 64% polymorphonuclear cells (1% eosinophils), 34% lymphocytes and 2% myelocytes. The urine was normal. The plasma proteins were 5·3 g. per 100 ml. with an albumin-globulin ratio of 5·6 to 1. Wassermann and Kahn reactions were negative. The pericardial fluid contained an average of 3 g. of protein per 100 ml. with 65 cells per c.mm., 85% lymphocytes. The pericardial fluid and gastric washings were sterile and the presence of tubercle bacilli could not be demonstrated on culture or on guinea-pig inoculation. The cerebrospinal fluid was normal. Throat swabs failed to grow pathogenic organisms. The only E.C.G. abnormality detected was an elevated RS-T segment. The dye and complement-fixation tests for toxoplasmosis

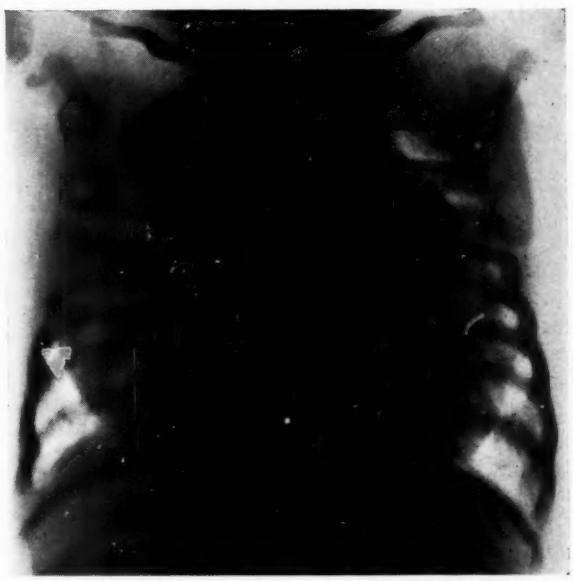

FIG. 1.—A grossly enlarged heart. Very little lung tissue is seen around the central density.

did not indicate an active infection. The antistreptolysin titre was less than 50 units per ml. Mantoux reactions up to 1 in 100 were persistently negative.

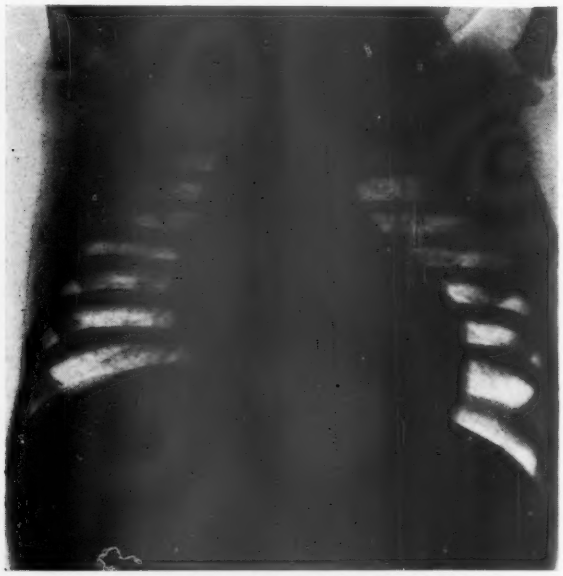

FIG. 2.—The heart shadow within normal limits.

Discussion

Descriptions of the syndrome all reveal a very similar clinical pattern. An upper respiratory tract infection very commonly preceded the onset of the pericarditis. The immediate prognosis is good, complete recovery taking place. Carmichael *et al.* (1951) have found a uniformly good prognosis in cases followed up for 15 years and more.

Various antibiotics alone and in combination with cortisone have been used in treatment (Friedman *et al.*, 1952; Martinez and Sariñana, 1950; Taubenhaus and Brams, 1950). It is doubtful, however, whether these drugs have any specific effect on the course of the disease.

The aetiology of the syndrome remains obscure. Among the more likely possibilities are tuberculosis, rheumatism, a hypersensitive response of the pericardium or a virus infection.

No evidence of tuberculosis could be found in this case. A search for a primary focus or contact proved fruitless. The tubercle bacillus could not be demonstrated in stomach washings or pericardial fluid. The Mantoux reactions were persistently negative.

None of the common associated criteria of rheumatism were present. An endocardial bruit was not detected at any stage. The serological evidence failed to substantiate a rheumatic aetiology.

Carmichael *et al.* (1951) found a large number of cases in their series with a personal or family history of allergy. Pericarditis, clinically indistinguishable from benign non-specific pericarditis, has been reported during serum sickness (McKinlay, 1948). In such cases, eosinophilia has been present; high counts of eosinophils have been demonstrated in the pericardial fluid. These findings were all absent in this case.

The syndrome has been observed in small epidemics in adults. Bing (1933) reported an epidemic of acute benign pericarditis in adults in Copenhagen, six cases being admitted to hospital within a few weeks. The frequent occurrence of an upper respiratory tract infection again suggests an infective origin. The pericardial fluid is invariably sterile. The presence of benign pericarditis in a systemic viral infection has been demonstrated in a case of lymphogranuloma venereum (Sheldon, Wall, Slade and Heyman, 1948). The favourable outcome, apparently uninfluenced by antibiotic therapy, would suggest a viral rather than a bacterial infection.

Summary

A case of acute benign pericarditis in an infant is described. The aetiology is discussed and the evidence in favour of a virus infection presented.

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CHRONIC REGIONAL ENTERITIS IN CHILDHOOD

BY

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Regional enteritis was first described by Crohn, Ginzburg and Oppenheimer in 1932. Although many adult cases of this condition have been described, there are few reports of chronic regional enteritis in childhood (Meade, 1941; Bockus, 1945; Koop, Perlingiero and Weiss, 1947; Oleson, 1952). Crohn (1949) reported six (2·7%) under 10 years of age out of a total series of 222 cases; Shapiro, Ravdin and Johnston (1939), in a review of the literature, gave an incidence of 4·7%, but did not indicate whether this figure included both acute and chronic cases.

The aetiology of chronic regional enteritis is still unknown. The pathological picture is one of chronic inflammation with healing by fibrosis which involves the whole intestinal wall and regional lymph nodes.

The purpose of the present paper is to describe two cases, one of which has been treated with corticotropin (A.C.T.H.).

Case Reports

Case 1. A boy, aged 10 years, was admitted to the Birmingham Children's Hospital on October 19, 1954. He had been well until 12 months before admission when he developed persistent diarrhoea; at times it became more severe but he usually had three or four brown, liquid stools daily containing mucus but no blood. He gradually lost weight and became lethargic and pale. It was noticed that he perspired at night and occasionally appeared feverish. There was no history of vomiting or abdominal distension.

On admission he was pale, underweight and looked ill. General examination revealed no other abnormality.

Peripheral blood examination showed a haemoglobin of 9·7 g. per 100 ml., red blood cells 4,200,000 per c.mm., white blood cells 12,600 per c.mm. with 78% polymorphs. The Mantoux (1 : 1,000 and 1 : 100 dilutions of old tuberculin) and Wassermann reactions were negative. Repeated stool examinations revealed no abnormality on microscopy or culture. The occult blood test was negative.

A radiological examination was made by Dr. R. Astley. A barium enema showed a narrowing of the proximal ascending colon and caecum. Retrograde flow into the ileum revealed a similar stenosis in the terminal few inches (Fig. 1). The narrowing ended abruptly and

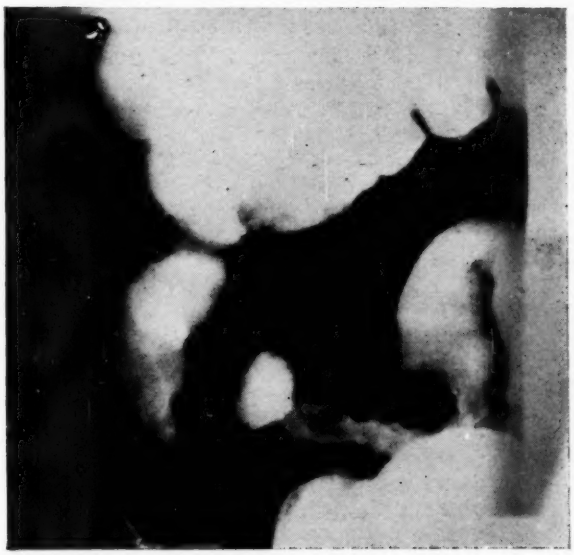

FIG. 1.—Barium enema showing terminal ileum, caecum and proximal ascending colon.

above this level the small intestine was slightly dilated. In the narrow area the outline of the bowel was rather shaggy and showed a close, shallow scolloping. A follow-through examination two days later confirmed these findings; there was very little obstruction to the passage of the barium.

During the first 17 days in hospital, despite rest in bed and a high-protein, low-residue diet with added vitamins, he continued to lose weight and the diarrhoea persisted.

A.C.T.H. was then begun, using the gel preparation by intramuscular injection once daily. The initial dosage was 40 units (approximately 1 unit per lb. body weight) for three weeks with gradual reduction of dosage thereafter; over 80 days he received 2,145 units of A.C.T.H. Ferrous gluconate and potassium chloride were also given orally. His appetite and general well-being improved and there was a gradual gain in weight (Fig. 3). Eighteen days after beginning A.C.T.H. he passed a normal formed stool. The stools have remained normal, usually with one bowel motion daily or every second day. The haemoglobin concentration slowly rose to 14 g. per

100 ml. The A.C.T.H. was discontinued when he developed a paronychia which responded to a five-day course of aureomycin.

A barium enema five weeks after stopping A.C.T.H. showed that there was still narrowing of the caecum and terminal ileum, but that the bowel now had a well defined although irregular outline, suggesting healing (Fig. 2).

FIG. 2.—Barium enema five weeks after stopping A.C.T.H. Appendix also demonstrated.

In places there were diverticula-like projections. At this examination the appendix, not previously demonstrated, was also seen to have an irregular but sharply outlined lumen.

Case 2. A boy, aged 12 years, was admitted to the Birmingham Children's Hospital on September 4, 1951. During the preceding nine months he had had recurrent attacks of vomiting which occurred on average two or three times a week, but were not associated with abdominal pain. He had progressively lost weight, lacked energy and become pale. The stools were normal.

On admission he was a pale, thin boy who looked ill; there was a tender palpable mass occupying most of the right iliac fossa.

Peripheral blood examination showed a haemoglobin of 8·8 g. per 100 ml., red blood cells 4,000,000 per c.mm., white blood cells 6,500 per c.mm. with 70% polymorphs. The Mantoux reaction was negative.

A barium enema demonstrated that the lumen of the caecum and ascending colon was narrowed to a small, irregular channel beyond which the contrast medium would not flow. A follow-through examination showed that the terminal ileum was also involved, with considerable dilatation of the small intestine more proximally, but no delay in transit. The narrowed bowel and the dilatation above it could be identified by gas shadows in direct radiographs of the abdomen.

Laparotomy was performed by Mr. R. K. Debenham on September 22, 1951. The palpable mass consisted of thickened, reddened, oedematous terminal ileum, caecum, a portion of the ascending colon and enlarged mesenteric lymph nodes. The distal ileum was dilated for several feet proximal to the mass. The terminal ileum (14 in.), caecum and ascending colon (2 in.) were resected and an end-to-side anastomosis performed; post-operative convalescence was uneventful.

A pathological examination was made by Dr. H. S. Baar.

The wall of the ileum showed a continuous thickening in a caudal direction, the proximal end having a thickness of 1 mm. and the distal end 6 mm. The wall of the caecum was also thickened. There were submucous haemorrhages in the distal part of the ileum along the mucosal folds. The appendix was embedded in fibrous tissue and its wall was extremely thickened up to 6 mm. At the ileo-caecal junction there was a plum-sized mass which consisted of enlarged lymph nodes and fibrous tissue. Most of this mass was, on the cut surface, white with pinkish-grey and ochre yellow areas.

The mass consisted of an extremely oedematous granulation tissue within which plain muscle fibres were enclosed. The appearance of the granulation tissue varied; some areas showed mainly capillaries and fibroblasts, others showed many eosinophil leucocytes, while in some areas there were dense, diffuse aggregations of reticulum cells or of plasma cells. In such areas giant cells of the Langhans type were seen, but there were only occasional circumscribed granulomata with giant cells. The appendix showed complete ulceration of its mucosa and the lumen was surrounded by granulation tissue. The central part of the latter was very cellular with reticulum cells, plasma cells and giant cells; the periphery consisted of oedematous, less cellular, granulation tissue with fibroblasts and eosinophil leucocytes.

The boy has remained very well since the operation and has gained weight normally, but does have an occasional loose stool.

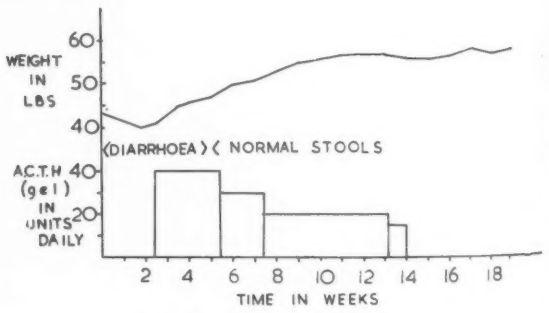

FIG. 3.—Progress in hospital.

Discussion

There have been many reported cases of acute regional enteritis in children (Erb and Farmer, 1935; Probstein and Gruenfeld, 1936; Mailer, 1938;

Harris, 1940; Meade, 1941; Ebrill, 1945; Storrs and Hoekelman, 1953). These cases have usually presented with symptoms and signs suggestive of an acute abdominal emergency, e.g. appendicitis, and the diagnosis has been made at laparotomy. Recovery in such is often complete and Storrs and Hoekelman, who reported eight cases with a long follow-up, believe that it is a specific entity unrelated to chronic regional enteritis. Other authors, however, suggest that some cases do progress to the chronic condition (Harris, 1940; Meade, 1941; Crohn, 1949).

Chronic regional enteritis, whilst a rarity in childhood, must be considered in the differential diagnosis of any subacute or chronic abdominal disorder. Our first case presented with chronic and persistent diarrhoea suggestive of ulcerative colitis and on abdominal examination there was no demonstrable pain, tenderness or rigidity and no tumour mass palpable. Bacteriological examination was negative for pathogenic organisms. The diagnosis was established by radiological examination. In the second case the clinical picture was strongly suggestive of a partial intermittent intestinal obstruction with a palpable mass in the right iliac fossa. This raised the suspicion of a chronic intussusception or an appendix abscess. Until now the most satisfactory treatment available has been surgical, the operations usually employed being resection of the diseased bowel or by-passing procedures which leave the affected segments *in situ* (Kirsner and Palmer, 1953). In many cases, however, operative results have been disappointing and recurrences frequent. The problem is that it is often difficult to determine with any degree of accuracy the extent of diseased bowel and how much of the bowel must be resected.

During the last few years several authors have reported some degree of benefit in adult patients by the use of A.C.T.H. and cortisone (Gray, Reifenstein and Benson, 1951; Machella and Hollan, 1951; Kirsner, Palmer and Klotz, 1952). In these patients the disease had been present for years and many had previously been submitted to surgical procedures of one kind or another. Consequently a striking degree of success could hardly be anticipated, but the results were certainly promising, and the pathological lesion appeared to be suppressed. This was the basis that led to a trial of A.C.T.H. in the first case here recorded, as it appeared that in this instance the duration of the disease could be measured in months rather than in years. The boy remained perfectly well and in complete remission for a total of seven months (five months after discontinuing the A.C.T.H.). He then suffered a relapse with abdominal pain, loss of appetite and weight, vomiting and diarrhoea. Oral cortisone was begun in a dose of 37·5 mg. b.d. and there has so far been a moderate but distinct improvement, but not the dramatic remission which was witnessed previously. Although there is still radiological evidence of considerable pathological change, some healing appears to be occurring. The ultimate benefit cannot yet be assessed, but in the light of this experience it is suggested that A.C.T.H. is worthy of trial in a child suffering from chronic regional enteritis before surgery is contemplated.

Summary

Two cases of chronic regional enteritis in children are reported. A.C.T.H. was used in one case and produced a rapid remission.

We wish to thank Professor J. M. Smellie and Dr. Frances Braid for advice and permission to publish these cases, and Mr. J. G. Williamson for the photographs.

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RETICULUM-CELL SARCOMA IN INFANCY

BY

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(RECEIVED FOR PUBLICATION APRIL 18, 1955)

With the exception of the leukaemias and tumours of the central nervous system any single type of malignant tumour is relatively uncommon in infancy and childhood, and few surgeons have extensive personal experience of the life history of these tumours.

A case is presented, first to show the difficulty of early diagnosis and secondly as an example of an apparent cure of a reticulum-cell sarcoma.

FIG. 1.—On the day following admission an antero-posterior radiograph shows an area of decalcification in the upper tibial metaphysis (August, 1948).

In August, 1948, at the age of 1 year, this baby girl was admitted to the surgical wards of the Royal Hospital for Sick Children, Glasgow, with a red, hot and painful swelling of the left leg of 10 days' duration. The temperature was 101° F. and the white blood count 8,000. A diagnosis of haematogenous osteitis was made, the limb was immobilized, and, after removing venous blood for culture, penicillin therapy was started. Radiography the following day revealed an area of decalcification in the upper tibial metaphysis (Fig. 1), and the bacteriologist reported a pure growth of coagulase-positive *Staphylococcus aureus* from the blood culture. Within three days the temperature was normal and the leg painless. Aspiration of soft tissue and bone marrow revealed neither pus cells nor organisms. Radiography three weeks after admission revealed separation of the upper tibia and fibula, more suggestive of tumour than of infection (Fig. 2). A biopsy was performed the following

FIG. 2.—Three weeks after admission, a radiograph shows sclerosis of the upper tibia and subperiosteal new bone formation. The lateral view shows separation of the tibia and fibula suggesting a diagnosis of tumour.

day and the pathologist reported the presence of a reticulum-cell sarcoma (Fig. 3). After consultation with the radiotherapist, deep *x*-ray therapy was started immediately. The tumour continued to grow and in January, 1949, radiography showed gross decalcification of the tibia and a large soft-tissue tumour (Fig. 4). The swelling increased rapidly and the general condition deteriorated. The child could neither eat nor sleep because of severe pain, and the almost hopeless nature of the condition was explained to the parents. They agreed to a palliative amputation to allow their child to die in relative comfort. Mid-thigh amputation was performed

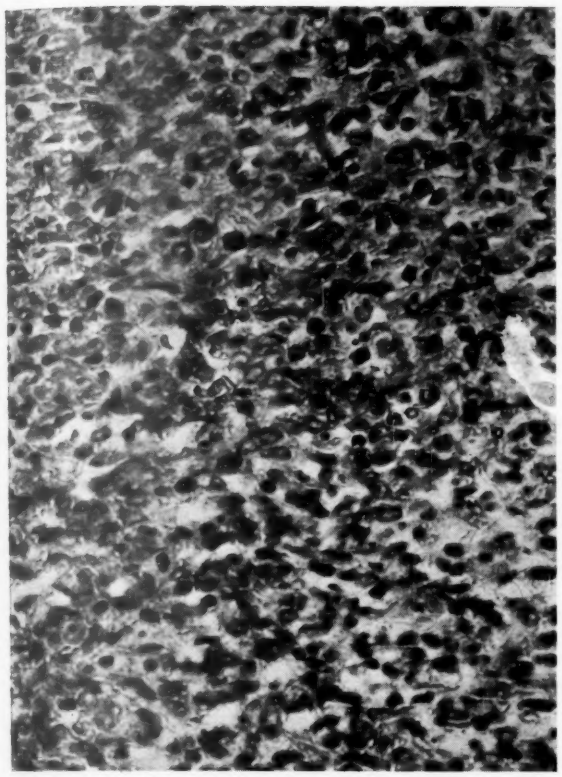

FIG. 3.—Photomicrograph (×250) shows rapidly growing sarcoma, highly vascular and invading muscle tissue. Tumour cells are producing reticulum or fibrous stroma suggesting a poorly differentiated fibro- or reticulum-cell sarcoma (confirmed by silver impregnation).

FIG. 4.—Radiograph taken in January, 1949. Massive soft-tissue swelling with gross decalcification of bone and possible destruction of the knee joint.

in February, 1949, five months after her first admission, and she made a rapid and uneventful recovery. She was comfortable and happy and rapidly put on weight, and

FIG. 5.—The patient in November, 1953.

the orthopaedic appliance department of the hospital made a temporary prosthesis. Four weeks after amputation she was toddling happily around the ward. An orthodox prosthesis was supplied in due course and five years after operation she is doing well at school and appears to be little handicapped by her artificial limb (Fig. 5).

Discussion

Even in retrospect the original radiographic appearances are quite compatible with a diagnosis of osteitis. With a temperature of 101° F. and a positive blood culture such a diagnosis would seem more likely than neoplasm. The amputation specimen shows that although the bone is hyperaemic and decalcified, the tibial cortex is intact and the tumour appears to arise from between the tibia and fibula. Further sections confirmed the biopsy report and the many pathologists who examined the sections all gave a grave prognosis. We know only too well the fate of all cases of leukaemia, of malignant tumours of the central nervous system, of sympathicoblastomata of the adrenal and of most children with nephroblastomata of the kidney and rhabdomyosarcomata of the bladder. Textbooks of surgery and pathology are singularly unhelpful with regard to the outlook in the less common malignant tumours of infancy and childhood.

Apart from the present child, there have been 11 five-year cures of malignant disease during the period during which she has been under observation. The lesions were all treated by excision and radiotherapy and were as follows: soft-tissue sarcoma (three cases), nephroblastoma (Wilms tumour) (four cases), neuroblastoma (one thoracic, one pelvic), testicular teratoma and ovarian dysgerminoma.

Under the auspices of the Scottish Surgical Paediatric Club, a paediatric tumour registry has been started. The paediatric units in Scotland, both medical and surgical, will pool their material and in time we may learn something of the life history of the less common malignant tumours of infancy and childhood.

Summary

A case of reticulum-cell sarcoma in an infant is described briefly. The patient was treated as a case of haematogenous osteitis for three weeks before the diagnosis was made. Few individuals have extensive experience of this type of case and the paediatric surgeons of Scotland have gained the whole-hearted cooperation of the pathologists in forming a paediatric tumour registry.

The photographs were prepared by Mr. J. L. A. Evatt, A.R.P.S.

PARTIAL ABSENCE OF THE TRACHEA WITH LIVE BIRTH

BY

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(RECEIVED FOR PUBLICATION JUNE 5, 1955)

Although anomalies of the trachea and oesophagus are not uncommon in paediatric practice, the case to be described is quite rare and no similar anomaly has been previously recorded at the Royal Hospital for Sick Children, Glasgow. Briefly, the condition is one of atresia of the larynx, partial absence of the trachea and a fistulous connexion between the oesophagus and the trachea. A point of considerable interest is that life was sustained for a short time and partial expansion of the lungs was achieved; but for the presence of much mucus in the lower respiratory passages life might have been prolonged further. A separate anomaly, namely extreme hypoplasia of one kidney, was also present.

The tracheal anomaly has already been recorded in the German literature by Fritz (1933) and similar but not identical cases have been described by Beneke (1905), Walcher (1928) and Kessel and Smith (1953). That described by Fritz is essentially similar to our case and occurred in a 43-cm. male infant who survived for about 12 minutes but failed to cry. Necropsy showed that a portion of the trachea 3 cm. in length was entirely absent, that the larynx was fully formed but completely atretic distally and that a small fistula passed downwards connecting the oesophagus, from a point 3·2 cm. below the incisura interarytenoidea, with the upper extremity of the formed trachea. The lungs were poorly expanded.

Fritz discusses briefly the anomalies of the trachea and oesophagus, comprising (*a*) simple oesophageal atresia, (*b*) oesophageal atresia with the distal portion in continuity with the carina, (*c*) tracheo-oesophageal fistula, (*d*) atresia of the larynx, (*e*) atresia of the larynx, partial absence of the trachea, the upper end of which is in continuity with the upper oesophagus while the lower part of the oesophagus takes origin at the carina, and (*f*) atresia of the larynx, partial absence of the trachea and oesophago-tracheal fistula.

The present case and that described by Fritz belong to this last category. A similar but not identical case was described by Beneke (1905) in which the larynx was small and atretic, the trachea entirely absent, and the bifurcation of the major bronchi opened into the oesophagus.

Walcher (1928) also describes a neonatal absence of the trachea in a female infant of body length 45 cm. and body weight 1,990 g. who survived for four days. Here a 2·5 cm. slit-like opening in the anterior wall of the oesophagus communicated with the tracheal bifurcation. No abnormality of the larynx other than atresia is described.

More recently Kessel and Smith (1953) describe a case of complete absence of the trachea with a fistulous connexion between the oesophagus and fused major bronchi. The larynx was normal but ended blindly below the level of the cricoid cartilage. The lungs were poorly expanded and histological sections showed large areas of atelectasis with extreme congestion, focal oedema and some alveolar haemorrhage. Kessel and Smith refer to no previous cases of complete or partial absence of the trachea but cite Wolman (1941) who gathered 10 cases of stenosis of the trachea and added one of his own, a female aged 2 months in whom the trachea tapered down from its laryngeal end to just above the bifurcation where the lumen measured only 1·5 mm. The cartilaginous rings completely encircled the trachea. The lungs showed oedema, small alveolar haemorrhages and were rather collapsed.

Case Report

The infant (R.H.S.C. HR 257/54), a male, was delivered spontaneously by a healthy mother who is Rhesus positive and has a negative Wassermann reaction. At birth the child was very blue and did not cry. He moved actively, however, and the air passages were cleared by suction. Afterwards 1 ml. of lobeline was given and respiration improved. Intragastric oxygen was then administered and this improved the child's colour. His respiratory rate was then 8 per minute. On auscultation a loud, harsh systolic murmur was heard

over the whole cardiac area. After 30 minutes intragastric oxygen was stopped and oxygen with 5% carbon dioxide given in an incubator. The respiratory rate was unchanged and the chest excursion poor. The heart beat was loud and forcible. A further 1 ml. of lobeline was given and the respiratory rate rose to 12 per minute. The child at no time cried, remained rather cold and its movement feeble. Fifteen minutes later the heart beat became faint and after a further 15 minutes the child died. He had survived for 4 hours and 42 minutes.

Necropsy showed a well-developed male infant of body weight 3,600 g. The mouth and tongue were normal. The oesophagus was congested and a 2-mm. diameter circular pit was noticed in the anterior wall at about its midpoint. A probe passed through here entered the lower trachea through its convex dome. The larynx was unfused posteriorly and contained much mucus. The vocal cords appeared normal. The lower end of the larynx was atretic and the proximal trachea entirely absent (Fig. 1). The lower trachea, normally canalized, began with a closed, smoothly rounded, dome-like convex extremity 2 cm. above the carina at about the level of the oesophageal fistula and bifurcated normally. Much mucus was present in the distal trachea, causing obstruction. The lungs were rather poorly expanded. The gastro-intestinal tract was normal. The right kidney and ureter were extremely hypoplastic, but the left kidney, ureter, bladder, prostate and testes were normal. The right adrenal was considerably larger than the left. The thyroid and pituitary were normal; the thymus (12 g.) was rather large but of normal appearance.

FIG. 1.—Macroscopic appearance of the air passages. The dome-like apex of the tracheal portion is seen with a probe passing into it from the oesophagus. The lungs are poorly expanded.

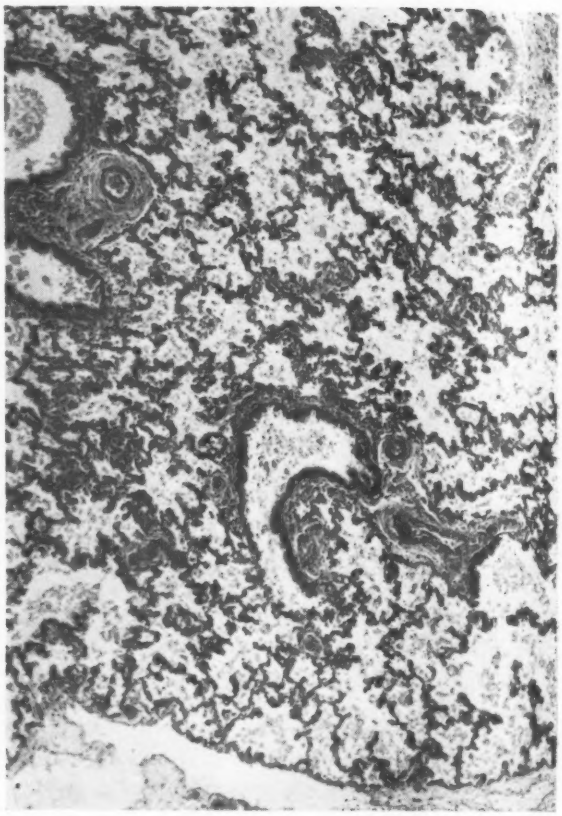

FIG. 2.—Section of lung showing some degree of expansion. Haemorrhages are present in many of the alveoli in this area. Haemalum and eosin × 60.

Histology of the heart, thymus, salivary glands, pancreas, spleen, testes, left kidney, medulla oblongata and cerebral cortex showed no significant lesion.

The adrenals presented rather prominent foetal zones.

The right kidney showed very few glomeruli or tubules, but occasional cysts were present in fibrous tissue.

The liver showed haemopoietic activity.

The lungs were unevenly expanded with alternating areas of emphysema and atelectasis. Neither these nor the trachea showed any evidence of infection. The alveoli contained occasional squames and macrophages. The vessels were congested and small focal alveolar haemorrhages were noted (Fig. 2).

Discussion

That anomalies of the trachea and oesophagus

should be common and of such considerable variety is more readily understood when the development of these structures is recalled. Frazer (1940) states that the pulmonary groove appears as a longitudinal sulcus in the floor of the foregut at the distal end of the primitive pharynx. The lower end grows backwards on the ventral side of the primitive oesophagus forming the rudimentary trachea. The trachea elongates after its separation from the oesophagus. This process of separation is not easily interpreted, but it appears that the long, slit-like opening into the oesophagus becomes shorter by the formation of an oesophago-tracheal septum made by fusion of lateral ridges from behind forwards. Little is added to this account by Hamilton, Boyd and Mossman (1945) or by Patten (1946). It can therefore be readily appreciated that anomalous development of the complex stages in this process may give rise to the various forms of tracheo-oesophageal abnormality mentioned briefly above.

In this instance it would appear that the upper portion of the pulmonary groove failed to form the tracheal tube, but that at the lower end the oesophago-tracheal septum formed normally. Both the lower trachea and the lower oesophagus therefore communicate with the proximal oesophagus. Life was sustained for some time in this child by oxygen passed through the oesophago-tracheal fistula and it would seem that the administration of intragastric oxygen would make this process easier. It is possible that life would have been longer sustained but for the accumulation of much mucus in the bronchi and distal trachea from which it could not escape.

It is interesting to recall the contention of Potter and Bohlender (1941), based partly on experimental findings and substantiated by two cases of respiratory anomaly, that the inflow and outflow of amniotic fluid is not essential for alveolar development. In one a mass of lung having no communication with the trachea developed alveoli and in the other the lung was also well developed despite tracheal obstruction by a malformed cricoid cartilage. In this case the lumen at this point was not more than 1 mm. in diameter. Potter and Bohlender claim that in the latter case such a small opening could not permit any considerable inflow and outflow of amniotic fluid. They conclude that the alveoli in the foetus probably contain tiny amounts of transudate from the alveolar walls. The case of partial absence of the trachea just described would appear further to justify their thesis, although some small flow of amniotic fluid into the lungs must have occurred via the oesophagus as squames were found in the alveoli.

Summary

A case of a rare anomaly in the upper respiratory passage is described. Atresia of the larynx, partial absence of the trachea and oesophago-tracheal fistula were present. Nevertheless, the lungs were well formed and partially expanded. Life was sustained for a short time. An associated anomaly was extreme hypoplasia of one kidney.

I am indebted to Dr. J. P. O. Erskine, of the Overtoun Maternity Hospital, Dumbarton, for permission to quote from his clinical records, and to Mr. W. Mason, F.I.M.L.T., for technical assistance and for photographs.

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BOOK REVIEWS

Studies on the Nutritive Value of Bread and on the Effect of Variations in the Extraction Rate of Flour on the Growth of Undernourished Children. (M.R.C. Spec. Rep. Series No. 287.) By E. M. WIDDOWSON and R. A. MCCANCE. (Pp. 137; illustrated. 8s. 6d.) London: H.M. Stationery Office. 1954.

The earlier work of the research unit set up at Wuppertal to investigate the effects and treatment of undernutrition will be familiar to paediatricians in this country, and the publication of the present report is most welcome. The reader's first reaction will perhaps be the realization that children, compared to rats, are very poor experimental animals. The slowness of human growth and the impossibility of maintaining experimental conditions, even in an orphanage, when conditions are changing in the outside world are only two of the problems facing the investigator. The authors are the first to urge caution in drawing conclusions from their results. Nevertheless, they have accumulated a mass of interesting data, often conflicting with the findings of other observers, and their critical discussions of methods, planning of experiments, and possible causes of discrepancies provide invaluable and much-needed guidance in the scientific assessment of such work. While the various aspects of the problem studied are too numerous to be summarized briefly, it may be said that this monograph will amply repay careful study by anyone planning human nutritional or growth studies in the future, or wishing to evaluate similar studies undertaken in the past.

Advances in Pediatrics; Volume VII. Edited by S. Z LEVINE. (Pp. 351; illustrated. 62s.) Chicago: The Year Book Publishers (distributed in the U.K. by Interscience Publishers, London). 1955.

The authoritative monographs in this latest volume of *Advances in Pediatrics* are as welcome as their forerunners. Caffey writes on fibrous defects in the cortical walls of growing tubular bones; Meredith Campbell on the urinary tract; Gómez, Galván, Cravioto and Frenk on malnutrition with special reference to kwashiorkor; Edgar Mannheimer on phonocardiography; Perlstein on infantile cerebral palsy; Schwachman, Leubner and Catzel on fibrocystic disease of the pancreas, under the name of mucoviscidosis, and Swenson on congenital megacolon. If the titles of the monographs do not indicate their authors, at least the authors' names leave the reader in little doubt as to what their subject matter will be. The eminence of the people writing on their chosen subjects is a guarantee that what they have to say will be well worth attention and it would be invidious to single out any of these seven articles for particular comment.

It is perhaps a pity that five of the articles are from the United States, but in view of the subjects chosen this is scarcely surprising. The editors are to be congratulated on their choice of subjects of such topical interest.

Disglucogenosis. By J. POU DIAZ; foreword by S. van Creveld. (Pp. 192; 53 illustrations. Pesetas 100.—.) Sevilla: Publicaciones de Revista Espanola de Pediatria. 1954.

Few clinicians will see many cases of glycogen disease and certainly they will not see the various forms of it which have been described from time to time. The literature on the subject is very scattered and textbooks give only a very general picture of the condition. This monograph has been compiled from all the papers published since van Creveld's paper in 1929. There are in fact 325 references. The author has been at great pains to see that each writer is given full credit for his work or opinions in the body of the text, hence the book cannot be read as a dissertation on the disease. It is, however, a valuable reference book particularly to the physician meeting the condition in one of its more unusual forms. There is a full description of the various types, the hepatic, hepatomegalic, cardiomuscular, and nervous. There is a section on the biochemistry and histopathology and chapters on differential diagnosis and aetiopathogenesis. The latter is perhaps rather academic and abstruse. The writer describes a case of his own in considerable detail, adding one more case to the literature. There are some rather speculative sections, such as the one dealing with glycogen disease and the syndrome described by Mauriac of hepatomegaly in diabetic children associated with stunted growth. These, however, will provide a certain stimulus to anyone making a deep enquiry into aetiology.

The book can certainly be recommended to anyone dealing with a case presenting unusual manifestations. There will certainly be some part of the book which will throw light on the problem.